American Journal of Diseases of Children

VOLUME 55 JANUARY 1938 NUMBER 1

COPYRIGHT, 1938, BY THE AMERICAN MEDICAL ASSOCIATION

STUDIES OF FETAL RESPIRATORY MOVEMENTS

I. HISTORICAL AND PRESENT DAY OBSERVATIONS

BARNET E. BONAR, M.D.†

CHARLES M. BLUMENFELD, M.D.

AND

CON FENNING, M.D.

SALT LAKE CITY

In the past year or two there has been renewed interest in the study of fetal activity, particularly in respect to the so-called intra-uterine respiratory movements. Such activity was first reported years ago, but its existence as a physiologic phenomenon has never been settled to the satisfaction of all. Thus, in the latest edition of "Williams' Obstetrics"[1] it is stated that the conclusions regarding fetal respiratory movements have not been generally accepted and that doubt still exists as to the significance of some of the observations reported. In the light of new methods recently developed, renewed interest in the subject may serve to determine whether or not fetal respiratory movements in utero are physiologic and to solve some pertinent problems regarding the fetal and neonatal respiratory mechanism, some of which are the existence of a tidal flow of amniotic fluid in the respiratory passages of the fetus, the onset of neonatal respiration and the cause of fetal asphyxia. Practically, these investigations may help in gaging the effect of anesthetics and analgesics on the respiratory function of the fetus and the new-born infant.

In a monograph on the physiology of the embryo published in 1885 Preyer[2] reviewed the subject of intra-uterine respiratory movements.

From the University of Utah School of Medicine.

† Dr. Bonar died on Dec. 19, 1937.

1. Stander, H. J., in Williams, J. W.: Obstetrics, ed. 7, New York, D. Appleton-Century Company, Inc., 1936.

2. Preyer, W.: Specielle Physiologie des Embryo, Leipzig, T. Grieben, 1885. The following references were cited by Preyer: Schultze, B. S.: Der Scheintod Neugeborener, Jena, Mauke, 1871. Winslow, Scheel, and Herholdt, cited by Scheel, P.: De liquore amnii asperae arteriae foetum humanorum, cui adduntur quaedem generaliora de liquore amnii, Hafniæ, N. Christensen, 1798. Beclard, P. A.: Versuche, welche zu beweisen scheinen, dass der Foetus Fruchtwasser aspiriert, Deutsche Arch. f. Physiol. **1**:154, 1815. Geyl, A.: Intrauterine Inspirationen, Arch. f. Gynaek. **15**:388, 1880.

He stated that Vesalius in the sixteenth century noticed such movements, but only when the placental circulation had been interrupted. In 1781, in the fetuses of dogs and cats in which the umbilical cords had not been disturbed Winslow observed rhythmic dilatation and contraction of the nasal orifices, expansion and contraction of the thoracic wall and movement of the fetal abdomen in the amniotic fluid after the uterus had been exposed. He wrote, "Liquor amnii respirare videtur." Scheel in 1798 stated that the amniotic fluid is regularly present in the trachea and that it is aspirated with the first inhalation of air. Herholdt came to the same conclusion as a result of research on animals and expressed the thought that, although the fluid often escapes by itself, sometimes its expulsion has to be assisted, in order that normal respiration may be established after birth. To do this, not only must the mucus be removed, but the new-born infant must be placed in a position which will let the amniotic fluid run out. Beclard in 1815, according to Preyer, opened the uteri of animals late in pregnancy and saw the fetuses undergo respiratory movements which were slower than those after birth. Each inspiration was characterized by opening of the mouth, dilatation of the nostrils and elevation of the wall of the chest. These movements were faster and stronger the greater the disturbance of the placental circulation. If the neck of the living fetus was tied before the amniotic sac was opened, a fluid similar to amniotic fluid was found in the respiratory passages. If an aqueous solution of fuchsin was first injected into the amniotic sac, colored fluid was found in the bronchi after the neck had been tied. Geyl in 1879 injected an aqueous solution of aniline blue into the amniotic cavities of four fetuses situated in one horn of the uterus of a rabbit ten days before term, and made no injections into the three in the other horn. Three days later a litter of three dead and four living rabbits was delivered. The three dead and one of the living animals had blue-stained patches in the lungs. Preyer himself observed a few respiratory movements in the fetuses of guinea-pigs with intact amniotic sacs which had been immersed in warm saline solution. After a long wait the freed fetuses breathed normally, thus showing that they could recover from inspired amniotic fluid. Preyer expressed the thought that a fetus cannot make respiratory movements until it has acquired reflex irritability and that undoubtedly amniotic fluid is inhaled into the alveoli of the lungs by premature respiratory movements.

In 1888 Ahlfeld[3] described intra-uterine movements of the fetus which were rhythmic, periodic and repeated and which occurred from 38 to 78 times a minute. They were observed in the neighborhood of the umbilicus of the unopened abdominal walls of pregnant women.

3. Ahlfeld, F.: Die intrauterine Tätigkeit der Thorax-und Zwerchfellmuskulatur, intrauterine Atmung, Monatschr. f. Geburtsch. u. Gynäk. **21**:143, 1905.

His pupil Weber studied these movements and published curves obtained with a kymograph. In 1890 Ahlfeld again brought up the subject, postulating that the impulses observed were due to intra-uterine respiratory movements. The hypothesis was immediately attacked by Runge and others, who admitted seeing such movements only when the umbilical cord was compressed. Runge performed this act in sheep and concluded that respiratory activity occurs only in apneic fetuses. Others expressed the belief that Ahlfeld's observations dealt with pulsations of the abdominal aorta. Ahlfeld showed tracings in which the fetal respiratory movements, the maternal respiration and pulse and the time were recorded, but not simultaneously. He also showed curves

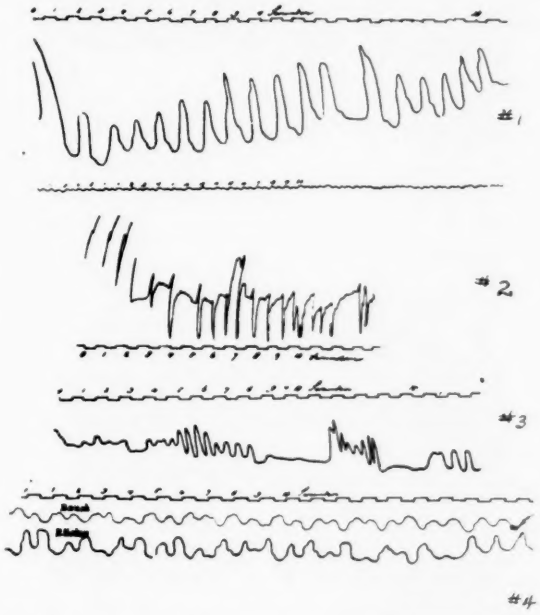

Fig. 1.—Ahlfeld's curves: ((*1*) intra-uterine respiratory and maternal pulse, (*2*) respiratory curve of the new-born, (*3*) periodic acceleration of intra-uterine breathing and (*4*) Intra-uterine fetal respirations taken simultaneously from the back and the abdomen of a fetus.

in which the fetal movements were obviously different from the aortic pulse of the mother. However, the majority of German obstetricians disagreed with his hypothesis, and the controversy remained unsettled, in spite of the fact that Ahlfeld again brought up the subject in 1905 and corroborated his original observations (fig. 1). It is most important to note that he was able to obtain curves which showed that as the thorax rises it contracts. He expressed the belief that the movements are superficial and that they suffice for inhaling amniotic fluid to the tracheal bifurcation and then expelling it. He also stated that the

movements in general are necessary for the normal development of the respiratory muscles.

Reifferscheid [4] in 1911 stated that he was able to observe movements in the umbilical regions of women late in pregnancy. They appeared to arise from the fetal thoracic region and even by observation were not synchronous with the maternal pulse or respiration. To prove this, simultaneous kymographic tracings were made with markers which registered time, maternal respiration, maternal carotid pulse, and fetal movements. The curves (fig. 2) demonstrated positively that the maternal pulse is not responsible for the movements and that they are

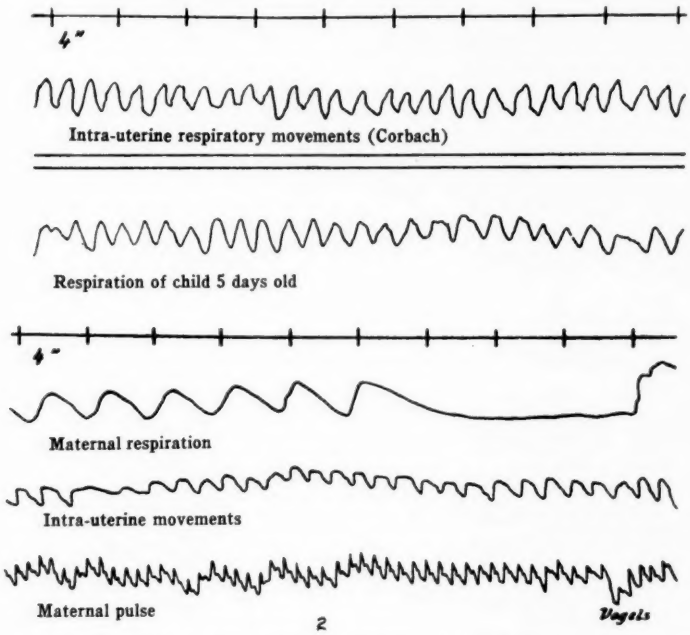

Fig. 2.—Reifferscheid's kymographic curves: (*1*) intra-uterine and neonatal respirations and (2) simultaneous tracing of maternal respirations, fetal intra-uterine respirations and maternal pulse.

too regular to be due to ordinary fetal movements. If the fetal position changed, the movements being recorded ceased suddenly, and if the funnel was placed over the new position assumed by the fetus, the movements again appeared in the tracing. From the evidence thus obtained, Reifferscheid was convinced that the movements arise from the thorax of the fetus. Because of their regularity and frequency, he expressed the belief that they must be physiologic. He concluded, in agreement with Ahlfeld, that this peculiar activity is due to fetal respira-

4. Reifferscheid, K.: Ueber intrauterine Atembewegungen des Foetus, Deutsche med. Wchnschr. **37**:877, 1911.

tory movements. The similarity in character and average rate between intra-uterine and extra-uterine respiratory movements, from 36 to 70 and from 36 to 84, respectively, offered further support for the contention. Reifferscheid expressed the opinion that the movements of the respiratory muscles occurred with the glottis closed. In spite of Reifferscheid's investigations, little attention was paid to the subject for some time. In 1920 Wislocki [5] stated that every one working on pregnant animals is aware that movements resembling respiration occur during the later months of pregnancy. He demonstrated that thirty minutes after a replacement injection of potassium ferrocyanide and iron and ammonium citrates these substances can be seen in the trachea and lungs of a fetus. He concluded that amniotic fluid is normally inspired or aspirated into the trachea and lungs by a fetus during the latter half of pregnancy. In 1933 Klemperer [6] reported that he was unable to observe these movements consistently. He used anesthetized animals in which the uterus was exposed. Reifferscheid had previously offered an explanation for the failure of investigators to observe the movements with any degree of regularity in animals prepared in this way. He stated that, when the uterus is opened and the fetus exposed, physiologic conditions no longer prevail. The exposure, he said, constitutes a tremendous peripheral stimulus to the fetus. Because centers with low thresholds of irritability are paralyzed by strong stimuli and will for a while react only to excessive stimulation, it seemed reasonable to him to suppose that the respiratory center, which has a low threshold, will not react to the weak stimulus from the blood unless it is augmented by compression of the umbilical cord, which, some observers found, will initiate fetal respiratory activity. In the light of subsequent events, this observation does not seem to hold good. Klemperer's failure, in all probability, was dependent on his use of an anesthetic which depressed the fetal respiratory mechanism. He also demonstrated starch and iodine in the respiratory passages of fetuses into the amniotic cavities of which the substance had been injected.

In 1936 Rosenfeld and Snyder [7] anesthetized the abdominal and perineal regions of rabbits by transecting the lumbar portion of the spinal cord. After partial immersion of the animal in Ringer's solution at body temperature, the abdomen was incised and the uterus exposed. They observed fetal respiratory movements similar to those noted by some of the earlier investigators who did not use anesthetics (Winslow,

5. Wislocki, G. B.: Publication 274, Carnegie Institution of Washington, 1920.

6. Klemperer, H. H.: Experimentelle Studien zur Physiologie des ersten Atemzuges, Arch. f. Gynäk. **154**:108, 1933.

7. Rosenfeld, M., and Snyder, F. F.: Fetal Respiration in Rabbits, Proc. Soc. Exper. Biol. & Med. **33**:576, 1936.

Beclard). The movements were characterized by rhythmic excursions of the thorax and abdomen, which, while shallower, resembled qualitatively the respiratory act in the new-born offspring. Fetuses within the same uterine horn showed great variation in respiratory activity, some being quiescent while others exhibited the movements at rates up to 60 per minute. These investigators expressed the thought that the movements were not initiated by the operative procedure, because they could be seen after careful observation of the abdominal walls of pregnant animals who had not been subjected to operation. Using ether, paraldehyde, soluble phenobarbital U. S. P. (sodium phenobarbital) and pentobarbital sodium in amounts that did not impair the maternal respiration but caused light anesthesia, they found that the intra-uterine respiratory movements were either depressed or inhibited completely. They took motion pictures of these movements, which were exhibited by Eastman [8] at the meeting of the American Academy of Pediatrics.

A number of investigators have reported the presence of material from the amniotic sac in the lungs of new-born infants. Thus, Browne [9] found such material in the lungs of new-born infants dying of pneumonia and expressed the belief that the cause of the disease is aspiration of amniotic fluid infected after premature rupture of the membranes. Johnson and Meyer [10] reported that about 20 per cent of the 500 autopsies on nonviable and viable fetuses revealed evidence of pneumonia. The cause of the disease was ascribed to aspiration of infected amniotic fluid. In this series were 39 infants manifesting no pneumonia but having an excessive amount of material from the amniotic sac. Thirty-one of this group were stillborn. Of 124 infants who had lived from two hours to five weeks Farber and Sweet [11] demonstrated material from the amniotic sac in the lungs of 88 per cent. They attributed these findings to aspiration of amniotic fluid during intra-uterine asphyxia and were inclined to agree with Reifferscheid that the glottis of the fetus in utero is closed. Recently Snyder and Rosenfeld [12] have supported the opposite view, that inspiration of amniotic fluid is a normal function of fetal respiration. They injected india ink into the amniotic sac and after waiting a few minutes clamped the neck of the fetus. In fetuses that had been showing respiratory movements the lungs were blackened, while in quiescent fetuses such was not the case. Microscopic exami-

8. Eastman, N. J., in panel discussion on Cyanosis in the Newborn, J. Pediat. **9**:267, 1936.

9. Browne, F. J.: Pneumonia Neonatorum, Brit. M. J. **1**:469 (March 25) 1922.

10. Johnson, W. C., and Meyer, J. R.: Study of Pneumonia in Stillborn and Newborn, Am. J. Obst. & Gynec. **9**:151 (Feb.) 1925.

11. Farber, S., and Sweet, L. K.: Amniotic Sac Contents in the Lungs of Infants, Am. J. Dis. Child. **42**:1372 (Dec.) 1931.

12. Snyder, F. F., and Rosenfeld, M.: Breathing of Amniotic Fluid as a Normal Function of Fetal Respiration, Proc. Soc. Exper. Biol. & Med. **36**:45, 1937.

nation showed particles of carbon in the alveoli of the lungs of the former but not in those of the latter. They concluded that intra-uterine respiration is of functional significance in the development of the normal lung and serves to assist in the dilatation of the alveoli and elastic walls of the future air passages. Even Windle observed rhythmic respiratory movements in chicks, appearing normally about three days before they hatch.[13]

In the past year we have studied the fetal respiratory movements, using a technic somewhat similar to that of Rosenfeld and Snyder. Most of the observations were made through the exposed but intact uterus. However, in some cases the uterus was opened, in order that the fetal respiratory movements might be studied more closely through the transparent fetal membranes. In a few instances the outer chorionic layer was opened, in order that some of the reflected light, which at times obscured the view, might be eliminated. Instead of ordinary black and white film, color film (Kodachrome or Kodachrome A) was used with the appropriate lens filters. Use of color film made identification of tissue easier. Artificial illumination was furnished by four 750 watt photoflood Mazda lamps so arranged that they could be adjusted as desired. The camera was fixed at 2 feet (90 cm.) from the object when the 1 inch (2.5 cm.) F. 1.9 lens was used and at 3¾ feet (114 cm.) when the 3 inch (7.6 cm.) F. 4.5 telephoto lens was used. Exposures were made with a 16 mm. Eastman Ciné-Kodak at sixteen frames per second with an aperture of F. 2.8 for the ordinary lens and F. 4.5 for the telephoto lens.

Using this technic, we made the following observations on ten rabbits, five dogs and thirteen white rats.

1. *Fetal Respiratory Movements.*—Periodic rhythmic excursions of the fetal thorax and abdomen were observed through the intact uterus. There appeared to be no synchronous action between the different fetuses, some remaining quiet while others were active. Usually the respiratory movements were of about the same amplitude, but the rate varied considerably. Sometimes all fetuses were inactive for a short time. One rabbit was observed for more than one and one-half hours, during which time, save for a two-minute pause, one fetus manifested these movements uninterruptedly. At times as many as three or four fetuses showed respiratory activity. The movements were affected by several factors. In premature fetuses the activity was not as great in rate or amplitude as in animals at full term. The movements often stopped, or at least could not be observed, when the fetus kicked or squirmed about. During intense uterine contractions, the movements

13. Windle, W. J.: Some Factors Governing Initiation of Respiration, Anat. Rec. (supp. 3) **67**:54 (March 25) 1937.

ceased or were considerably reduced or obscured. Subsequently the rate was usually increased. The thoracico-abdominal movements did not appear to be disturbed when the uterus was opened and the amniotic sac exposed, unless, as happened several times, the placenta became detached. Viewed through the transparent fetal membranes, the respiratory act of the fetus resembled closely that of a newly born animal. Either the chest was raised upward suddenly while the abdomen retracted, or the abdomen expanded and there was retraction of the chest. The ribs moved upward and downward in much the same manner as in the neonatal animal, except that expansion was greatly curtailed. In most instances the respiratory movement was accompanied by alternate opening and closing of the mouth and dilatation of the nostrils. Three distinct types of movement were noted. The first was a rhythmic and regular act of relatively uniform amplitude, unaccompanied by any other active fetal movement. The second consisted of a series of crescendo-like movements followed by pauses similar to the apnea which follows rapid respiration in the new-born animals. The third resembled an asphyxial gasp, in which the mouth was opened wide if the excursion was violent. Movements of this sort usually were not rhythmic and were preceded or accompanied by active movements of the limbs and the body. The fetus appeared to be struggling for breath and actually tried to bite through the membranes. When the umbilical cord was clamped, increased fetal and respiratory activity was usually, but not always, observed. The width to which the mouth was opened seemed to depend on the intensity of the respiratory movement.

Light ether anesthesia stopped the fetal respiratory movements within five minutes, but fetal response to tactile stimulation usually remained. At the beginning of the anesthesia the rate was increased. Within from five to ten minutes after withdrawal an occasional respiratory movement could be detected, and in fifteen or twenty minutes respiratory activity had become regular again, although the rate remained slower and the amplitude less. In some animals, during the period of activity which often occurs as they are coming out of ether anesthesia, there was a short period of heightened respiratory activity on the part of the fetus. At this time the respiratory rate was extremely variable.

Sodium amytal (sodium iso-amylethyl barbiturate) was administered in doses sufficient to produce analgesia and drowsiness. At first the fetal respiratory rate was increased somewhat, but within ten minutes it was reduced, and the excursions were decreasingly uniform. Within fifteen minutes the movements were still more shallow, about every fourth one being of normal strength. Rhythmicity, however, continued. In one instance the movements ceased for two minutes after forty-two minutes, and then were resumed at a rate reduced by one-half, with

every fourth movement definitely stronger than the rest. In this fetus the movements continued for more than one and one-half hours and were still going when the experiment was stopped.

The respiratory rate varied greatly in different fetuses, in those of different species of animals and in those of different maturities. In general, the rate in dogs was less than that in rabbits or in rats, and in premature fetuses it seemed slower than in ones at term. Variations of from 4 to 90 beats per minute were observed. Ether rapidly reduced the rate and finally caused its cessation. Small doses of sodium amytal slowed it gradually. For instance, rates of from 30 to 40 per minute were slowed to from 10 to 15 and finally to cessation.

Through the unopened abdomen of a guinea-pig, we observed fetal activity resembling the rhythmic respiratory movements previously mentioned. We have also been able to see the movements of the abdominal walls of pregnant women which were described by Ahlfeld and Reifferscheid. When these movements occur, the women are able to feel them.

2. *Uterine Contractions.*—In some animals operated on at term, uterine contractions were so vigorous that they interfered with both the observations and the photography of the fetal respiratory movements. In two rabbits, labor commenced during the course of the experiment. Uterine activity was not as marked in animals a few days before term or in those to which theelin had been administered to prolong the period of gestation. Ether anesthesia diminished the rate and the intensity of uterine contractions and finally caused their cessation. Sodium amytal reduced the rate and the intensity also.

COMMENT

It seems odd, in view of the literature on the subject, that greater interest has not been manifested and more definite information obtained about intra-uterine fetal respiratory movements. Possibly there is an explanation for this. In the latter part of the eighteenth century and the early part of the nineteenth, general anesthesia was not in use, so that, when a few investigators observed these movements through the excised uterine walls of experimental animals, the fetuses were not depressed by anesthetics. When Ahlfeld noted through the abdominal walls of pregnant women the impulses which he considered due to fetal respiratory activity, no anesthetic had been given. Attempts to check this by opening the abdomens and uteri of anesthetized experimental animals resulted chiefly in failure to observe fetal respiratory movements. This probably led to the doubt about the existence of such activity and to the paucity of studies of the problem which has prevailed for years. The use of transection of the spinal cord by Rosenfeld and Snyder to anesthetize the lower part of the body and the consistent

observation by them of fetal respiratory activity again bring up the question of its physiologic existence. While transection of the cord may interfere considerably with the innervation of the uterus, it is unlikely that this alone would be sufficient to affect the fetus much. Immersion of the incised portion of the animal in physiologic solution of sodium chloride at body temperature should satisfy the criticism that exposure of the uterus to air might be responsible for respiratory activity. Furthermore, movements which appear similar to those observed in the exposed uteri of animals with transected spinal cords have been noted through the unopened abdominal walls of experimental animals. Similar observations have been made in pregnant women near term. The data presented here point to the existence physiologically of fetal respiratory movements. While Ahlfeld's kymographic tracings may be criticized because records were not made of maternal pulse and respirations at the same time, the work of Reifferscheid, who made simultaneous tracings, should be sufficient to meet the objections of critics. From a purely physiologic standpoint it would seem somewhat unreasonable, after all, to assume that the fetal respiratory tract remains inert in utero, awaiting some stimulus to initiate its hitherto unpracticed respiratory mechanism at birth, while the cardiovascular system, with which it is so intimately related, the gastro-intestinal tract and the kidneys function in utero. The suggestion that the movements are due to singultus does not seem to be an explanation, for hiccup occurs at a slower rate and is not as superficial an act. Furthermore, if singultus exists, the respiratory mechanism is capable of functioning. Especially is this so if singultus is a reflex act, for then it shows that the respiratory center is irritable.

Another question must be considered, namely, is there a tidal flow of amniotic fluid in the fetal respiratory passages? The reports of older investigators and the recent one by Snyder and Rosenfeld suggest that this is the case, since dyes injected into the amniotic sacs of fetuses were demonstrated a short time later in their lungs, after care had been taken to prevent their being inhaled when the animals were exposed to air at delivery. The knowledge that material from the amniotic sac is commonly found in the lungs of infants dying after birth is also a fair indication that this may be true. Furthermore, it is known that inspiration of amniotic fluid at birth is often nearly inevitable and is usually unattended by much danger. A number of investigators who have noted respiratory movements of fetuses in the amniotic cavity have subsequently delivered the infants and watched them breathe in a normal, unasphyxiated manner and continue to thrive. Some have suggested that the glottis remains closed in utero. This theory has never been proved, and at present the preponderance of evidence is against it. Moreover, a closed glottis would be inconsistent with the presence of respiratory movements from either an anatomic or a physiologic stand-

point. Finally, the whole hypothesis that the fetal respiratory tract remains inert in utero necessitates the assumption that the respiratory center is depressed. A satisfactory explanation of the cause of this has never been made. Therefore, in view of this and the findings related here, it seems to us that the easiest and most logical concept is that, in all probability, the fetal respiratory mechanism functions physiologically in utero. At least the acceptance of this hypothesis avoids the necessity of explanations so far unproved.

Whatever the final solution of the whole question, the present renewed interest should result in a decision, one way or another, which will be of practical value in attacking problems of fetal and neonatal morbidity and mortality. The chief difficulty, as we see it, is that the methods so far used to detect fetal respiratory movements have not been sufficiently accurate to meet the objections of critics. There is a distinct need for a better graphic method with which to meet these objections. At the present time we are working with an instrument which we hope will meet this need.[14]

SUMMARY AND CONCLUSIONS

As a result of a review of the literature on the subject and our own investigations, which have largely corroborated the observations of other investigators, we are inclined to agree with them that:

1. Intra-uterine fetal respiratory movements which simulate the neonatal respiratory act are probably physiologic.

2. Anesthetics, such as ether and sodium amytal, appear to have a depressing effect on these movements.

3. There is probably a physiologic tidal flow of amniotic fluid in the respiratory passages in utero.

Further study is needed, not only to decide these questions positively but to determine more accurately the effect of anesthetics and analgesics on the fetal respiratory tract and their relation to neonatal morbidity and mortality.

Present methods may be criticized because they are not accurate enough. The need for a better graphic method possibly may be met in the near future by a device with which we are working at the present time.

University of Utah.

14. Fenning, C.: A New Method of Recording Physiologic Activities: I. Recording Respiration in Small Animals, J. Lab. & Clin. Med. **22**:1279 (Sept.) 1937. Fenning, C., and Bonar, B. E.: A New Method of Recording Physiologic Activities: II. Simultaneous Recording of Maternal Respiration, Intrauterine Fetal Respiration and Uterine Contractions, ibid. **22**:1280 (Sept.) 1937.

INFLUENCE OF VITAMIN C ON DIPHTHERIA TOXIN

JEAN PAKTER, M.D.
AND
BÉLA SCHICK, M.D.
NEW YORK

In 1930 Szent-Györgyi [1] demonstrated conclusively that the hexuronic (cevitamic) acid isolated from the adrenal glands and crystalline vitamin C are identical. This discovery aroused much interest in the relation between vitamin C and the adrenals. Many workers [2] agreed that the adrenals of various animals are among the organs of the body richest in this vitamin. It was a logical step, then, to study the rôle of vitamin C in diseases associated with marked pathologic changes in the adrenals.

Prominent among these maladies is diphtheria. It has been known since 1889 that the adrenals suffer in severe diphtheria. Roux and Yersin [3] at that time showed that intense congestion of the adrenal glands can be brought about in guinea-pigs by means of experimental diphtheria. Wybaw,[4] Oppenheim,[5] Moltschanow [6] and others studied the pathologic picture of the adrenals in diphtheria, describing hemorrhagic and degenerative lesions. Oppenheim made extensive studies of guinea-pigs with experimental diphtheria with respect to the antitoxic

---

1. Szent-Györgyi, A.: Observations on the Function of Peroxidase Systems and Chemistry of Adrenal Cortex: Description of a New Carbohydrate Derivative, Biochem. J. **22**:1387-1409, 1928; On the Function of Hexuronic Acid in the Respiration of the Cabbage Leaf, J. Biol. Chem. **90**:385-393 (Jan.) 1931; On the Mechanism of Biological Oxidation and the Function of the Suprarenal Gland, Science **72**:124-126, 1930; Experiments Concerning Function of Adrenal Cortex and Mechanism of Biological Oxidation, Magyar orvosi arch. **28**:138-143, 1927.

2. (*a*) Giroud, A., and Leblond, C. P.: Répartition et évolution de la vitamine C dans l'organisme. Notions de carence précarence et déficience chimiques, Presse méd. **43**:1085-1087 (July 6) 1935. (*b*) Yavorsky, M.; Almaden, P., and King, C. G.: Vitamin C Content of Human Tissues, J. Biol. Chem. **106**:525-529 (Sept.) 1934. (*c*) Svirbely, Joseph L.: Ascorbic Acid Content of Adrenals and Livers of Different Animals, Biochem. J. **27**:960-963, 1933.

3. Roux, E., and Yersin, A.: Contribution a l'étude de la diphtherie, Ann. Inst. Pasteur **3**:273-288 (June) 1889.

4. Wybaw, cited by Stutzer.[9]

5. Oppenheim, Robert: La fonction antitoxique des capsules surrénales, Thèse de Paris, no. 231, 1902, pp. 7-166.

6. Moltschanow, W. J., cited by Stutzer.[9]

function of the adrenal glands. Marie,[7] Abramow and Mischennikow [8] and others studied the effect of epinephrine on diphtheria toxin. Marie found that it neutralized the toxin in vitro but not in vivo. The neutralization occurred only at 37 C. and after prolonged contact between the substances. Abramow and Mischennikow also found that prolonged periods of incubation of the toxin-epinephrine mixture were necessary for neutralization. Stutzer [9] noted that only commercial epinephrine which contained acid impurities could neutralize the toxin. When this acid epinephrine was neutralized it lost its detoxifying power. Schick, von Gröer and Kassowitz [10] found that commercial epinephrine (and pituitary extract) were strongly acid and because of this were capable of destroying toxin. Previous interpretations that the adrenals and the pituitary are concerned in the production of antitoxin were therefore faulty.

Recently much experimental research has been done to determine the effect of vitamin C (cevitamic acid, or ascorbic acid) on diphtheria toxin. Harde and Philippe [11] mixed one or two lethal doses of diphtheria toxin with solutions of from 100 to 200 mg. of vitamin C, allowed the mixture to stand from forty-five to sixty minutes at room temperature and then injected it into guinea-pigs. The test animals lived, while the control animals died in from four to eight days. Another group received injections of diphtheria toxin diluted with similar amounts of physiologic solution of sodium chloride. These guinea-pigs were able to resist one lethal dose of toxin but not two. A third group received vitamin C by mouth or subcutaneously and then was given from one and one-half to ten lethal doses of undiluted toxin. These animals did not survive. One year later Harde and Greenwald [12] repeated the work in a similar fashion. This time guinea-pigs which had been fed large amounts of vitamin C orally, subcutaneously or

7. Marie, A.: Glandes surrénales et toxi-infections, Ztschr. f. Immunitätsforsch. u. exper. Therap. **17**:420-431, 1913.

8. Abramow, S., and Mischennikow, S.: Ueber die Entgiftung bakterieller Toxine durch Adrenalin, Ztschr. f. Immunitätsforsch. u. exper. Therap. **20**:253-259, 1913-1914.

9. Stutzer, M. J.: Ueber die Wirkung von Adrenalin auf Bakterien und Diphtherietoxin, Ztschr. f. Immunitätsforsch. u. exper. Therap. **22**:372-380, 1914.

10. Schick, Béla; von Gröer, F., and Kassowitz, K.: Methodik und Technik der Erforschung der normalen antitoxischen Diphtherie-Immunität des Menschen, in Abderhalden, A.: Handbuch der biologischen Arbeitsmethoden, Vienna, Urban & Schwarzenberg, 1924, no. 3, pt. 2, pp. 503-546.

11. Harde, E., and Philippe, M.: Observations sur le pouvoir antigène du mélange toxine diphthérique et vitamin C, Compt. rend. Acad. d. sc. **199**:738-739 (Oct. 15) 1934; Anatoxine diphtérique et vitamine C, Compt. rend. Soc. de biol. **121**:940-942 (March 7) 1936.

12. Greenwald, C. K., and Harde, E.: Vitamin C and Diphtheria Toxin, Proc. Soc. Exper. Biol. & Med. **32**:1157-1160 (April) 1935.

intramuscularly did not survive after the administration of only one lethal dose. Harde attempted to explain the apparent discrepancy in results by stating that in the earlier work a freshly prepared toxin had been used which was unstable, which rapidly lost toxicity and "which also may have been more sensitive to vitamin C." A repetition of the in vitro experiments demonstrated a decrease in the toxicity of the toxin which had been mixed with vitamin C and allowed to stand one hour before injection.

Jungeblut and Zwemer [13] in 1935 investigated the effect of vitamin C on diphtheria toxin in guinea-pigs. Vitamin C in varying quantities was combined with diphtheria toxin, and the mixtures after standing one-half hour at room temperature were injected subcutaneously. Another group of guinea-pigs received subcutaneous injections of vitamin C and diphtheria toxin (two minimum lethal doses) at different sites. The authors stated that the in vitro experiments gave more precise and satisfactory results than the in vivo experiments in demonstrating the efficacy of the toxin-neutralizing power of the vitamin. Inactivation in vitro was done at a p_H of from 6.6 to 6.8. They also studied the effect of the storage of vitamin C in guinea-pigs on the reactions to intracutaneous injection of small doses of diphtheria toxin. They concluded that the storage of vitamin C has a pronounced effect in suppressing the local reaction to diphtheria toxin and that vitamin C plays an important rôle in natural resistance to diphtheria toxin. However, the results as shown in their tables were not conclusive enough to permit one to agree with their statement.

Von Jeney, Gagyi and Baranyai [14] also concluded that ascorbic acid has a detoxifying effect on guinea-pigs with experimental diphtheria. They stated that the vitamin C may play a rôle by virtue of biologic oxidation-reduction systems. Von Gagyi [15] mixed diphtheria cultures with solutions of vitamin C at a p_H of from 3.5 to 3.7 and found that the bacteria died in from one-half to six hours. Kliegler [16] showed that the addition of vitamin C to cultures of Bacillus diphtheriae inhibited the production of toxin. King and Menten [17] demonstrated

13. Jungeblut, C. W., and Zwemer, R. L.: Inactivation of Diphtheria Toxin in Vivo and Vitro by Crystalline Vitamin C (Ascorbic Acid), Proc. Soc. Exper. Biol. & Med. **32**:1229-1234 (May) 1935.

14. von Jeney, A.; Gagyi, J., and Baranyai, P.: Die mildernde Wirkung der Ascorbinsäure auf die Diphtheria Intoxication bei Meerschweinchen, Deutsche med. Wchnschr. **62**:54-56 (Jan. 10) 1936.

15. von Gagyi, Joseph: Ueber die bactericide und antitoxische Wirkung des Vitamin C, Klin. Wchnschr. **15**:190-195 (Feb. 8) 1936.

16. Kliegler, I. J.: Inhibitive Effect of Vitamin C on Toxin Production by C. Diphtheria, Nature **138**:291 (Aug. 15) 1936.

17. King, C. G., and Menten, M. L.: Influence of Vitamin Level on Resistance to Diphtheria Toxin, J. Nutrition **10**:129-155 (Aug.) 1935.

that the survival time for scorbutic guinea-pigs infected with diphtheria was half that for normal control animals. Harde [18] and others expressed the belief that a correlation exists between the ability of an animal to synthesize its own vitamin C and its insusceptibility to diphtheria. The example cited is that of the mouse, which is naturally resistant to diphtheria and synthesizes its own vitamin C in the body. Polónyi,[19] Mouriquand, Sedallian and Coeur [20] found that the vitamin C content of the adrenals diminished in guinea-pigs with experimental diphtheria. Mouriquand showed that the epinephrine content was likewise affected. Harde and Benjamin,[21] Yavorsky, Almaden and King,[2b] Lyman and King [22] and King and Menten [17] noted that the tissues of animals and human beings who had died of various infections and intoxications had a diminished vitamin C content.

Contrary to the aforementioned positive findings, negative results were obtained by Schwarz and Cislaghi.[23] These authors showed that the in vitro neutralizing effect of vitamin C was due to its acidity. The in vivo experiments failed to demonstrate any effects. Grooten and Bezssonoff [24] attempted to corroborate Harde's results. They concluded that the action of vitamin C on the toxin is not a specific one but is probably based on changes in the hydrogen ion concentration. The antitoxic action was shown to be feeble and inferior, manifesting itself only in the presence of such small doses of toxin that control animals were able to survive until the ninth day. The findings indicated to those authors that vitamin C does not act directly on diphtheria toxin. They suggested that huge doses of vitamin C might stimulate certain reactions of the organism and increase the general resistance, thereby explaining some of the positive results.

---

18. Harde, E.: Vitamines- acid ascorbique (vit. C) et intoxications, Compt. rend. Acad. d. sc. **199**:618-620 (Sept. 24) 1934.

19. Polónyi, P.: Einfluss des C-Vitamins auf den Krankheitserreger der Diphtherie, Wien. med. Wchnschr. **85**:685-686 (June 15) 1935.

20. Mouriquand, G.; Sedallian, P., and Coeur, A.: Intoxication diphtérique et acide ascorbique des surrénales, Presse méd. **43**:2113 (Dec. 28) 1935.

21. Harde, E., and Benjamin, H. R.: Vitamin C Content of Tissues of Laboratory Animals Under Various Pathological Conditions, Proc. Soc. Exper. Biol. & Med. **32**:651-653 (Jan.) 1935.

22. Lyman, C. M., and King, C. G.: Effect of Diphtheria Toxin on Vitamin Content of Guinea-Pig Tissues, J. Pharmacol. & Exper. Therap. **56**:209-215 (Feb.) 1936.

23. Schwarz, E., and Cislaghi, F.: Ricerche sperimentali su alcune azioni biologische dell' acido ascorbico sul potere antigene dei miscugli tossina difterica acido ascorbico, Minerva med. **2**:521-522 (Oct. 27) 1935.

24. Grooten, D., and Bezssonoff, N.: Action de la vitamine C sur la toxine diphthérique et sensibilité du bacille de la coqueluche vis-à-vis de l'hydroquinol et de la vitamine C, Ann. Inst. Pasteur **56**:413-426 (April) 1936.

Schick, von Gröer and Kassowitz [10] defined the properties of a true diphtheria antitoxin. They demonstrated that nonspecific destruction of the toxin might be caused by the following factors:

1. Strongly alkaline solutions.

2. Acid solutions: At a p_H of 5 the toxin becomes ineffective but not permanently damaged. (Commercial preparations of epinephrine and pituitary extract are strongly acid and, because of this, are capable of destroying toxin.)

3. Oxidation: Oxidizing agents and oxygen carriers have a deleterious effect on toxin. These effects characteristically take a long time to be realized.

4. Various proteolytic and peptolytic enzymes which inactivate the toxin.

5. Lipoids which bind the toxin.

6. High concentrations of saline solution.

7. Adsorption.

Schick, von Gröer and Kassowitz [10] gave ten criteria for determining a true antitoxin:

1. The antitoxic effect of true antitoxin is instantaneous on mixing.

2. The optimal p_H for effectiveness of antitoxin is slightly alkaline.

3. The neutralization follows multiples.

4. A true antitoxin is reversible. Both toxin and antitoxin may be reobtained from the union.

5. It neutralizes the same amounts of toxin from two different concentrations of the toxin.

6. It summates itself in its effect.

7. It is reversibly inactivated in acid solution.

8. Under 60 C. it is effective, becoming inactivated above that temperature.

9. It withstands ether extraction.

10. It is easily adsorbable.

None of the aforementioned authors could substantiate by these criteria their claims that vitamin C is a true antitoxin.

Because of the results of the reported experiments with guinea-pigs, it occurred to us to attempt to illustrate in human beings the effectiveness of vitamin C in neutralizing diphtheria toxin. Several workers [25]

25. (*a*) Bernhardt, H.: Ueber die Beeinflussung diphtherischer Kreislaufschwäche durch Nebennierenrindenhormon und Vitamin C, Deutsche med. Wchnschr. **62**:1123 (July 10) 1936. (*b*) Messer, H.: Beitrag zur Nebennierenrindentherapie bei Diphtheria, ibid. **62**:1131-1132 (July 10) 1936. (*c*) Ebel, A., and Mantner, H.: Experimentelle Beiträge zur Therapie der Diphtherie, Wien. klin. Wchnschr. **49**:464-465 (April 10) 1936. (*d*) Herbrand, W.: Die funktionelle und therapeutische Bedeutung des Nebennierenrindenhormons, Deutsche med. Wchnschr. **62**:1130-1131 (July 10) 1936. (*e*) Bamberger, P., and Wendt, L.: Ueber Beeinflussung diphtherischer Kreislaufschwäche durch Nebennierenrindenhormon und Vitamin C, Klin. Wchnschr. **14**:846-847 (June 15) 1935. (*f*) Aicham, A., and Bock, H.: Zur Beeinflussung der experimentellen Diphtherie durch Vitamin C und Nebennierenrindenextrakt, Monatschr. f. Kinderh. **65**:289-293 (April) 1936.

reported good results using vitamin C in conjunction with cortical extracts and diphtheria antitoxin in cases of clinically severe diphtheria. Obviously, statistics based on such uncontrolled surveys are well nigh useless for true scientific evaluation. We believed therefore that a more accurate approach would be to study the effects of vitamin C on the reactions to the Schick test of persons known to react positively to the test. It was planned to observe these effects in a manner akin to that used by Schick in 1912 in studying the relation between true diphtheria antitoxin and the reaction to the Schick test.[26]

Accordingly, we studied a group of children with positive reactions to the Schick test in our wards to see what effects could be obtained with vitamin C on the Schick reaction. All these children were convalescent and ready for discharge at the time the tests were done.

In the following tables we have used symbols to denote the extent of elevation and the degree of erythema of the Schick reactions, in addition to giving the actual diameters in millimeters. Slight erythema is expressed by a minus sign placed before the numeral denoting the diameter, and slight elevation, by a minus sign placed after the numeral. For example, an area measuring 20 mm. in diameter which was slightly erythematous and slightly elevated is indicated thus: —20—. Moderate erythema is expressed by an asterisk before the numeral, and moderate elevation, by an asterisk after the numeral. Marked erythema is expressed by a plus sign before the numeral, and marked elevation, by a plus sign after the numeral. The symbol before the numeral always denotes the degree of erythema, and the symbol after the numeral, the degree of elevation.

CASE 1.—E. S., a girl 5 years of age, had a strongly positive reaction to the Schick test; the area measured 20 mm. She was given 300 mg. of cevitamic acid by mouth for a period of one week in daily doses. At the end of this time the test was repeated. The reaction was as strongly positive as before. Apparently the oral administration of vitamin C had no effect on the reaction to the Schick test in this case.

In the cases reported hereafter we administered the vitamin parenterally, since adequate absorption might not occur if the oral route was used.

CASE 2.—H. C., a girl 4 years of age, received intravenously 300 mg. of cevitamic acid in the form of its sodium salt. Fifteen minutes later the Schick test was repeated. The results are shown in table 1.

26. (*a*) Schick, Béla; Kassowitz, K., and Busacchi, P.: Experimentelle Diphtherieserumtherapie beim Menschen, Ztschr. f. d. ges. exper. Med. **4**:83-148, 1914. (*b*) Michiels, J., and Schick, B.: Ueber die Wertbestimmung des Schutzkörpergehaltes menschlischen serums durch intracutane Injektion von Diphtherietoxin beim Menschen, Ztschr. f. Kinderh. **5**:349-354, 1912.

That the administration of vitamin C had no effect on the reaction is evident.

CASE 3.—M. K., a boy 9 years of age, received intravenously 300 mg. of cevitamic acid in the form of its sodium salt. Fifteen minutes later the Schick test was repeated. The results are shown in table 2.

Again there was no change in the reaction after the administration of the vitamin.

It occurred to us then that we should repeat the Schick test at varying intervals after the administration of the vitamin to insure sufficient time for the full absorption of the substance.

TABLE 1.—*Case 2*

	Diameter of Reaction to Schick Test After			
Injection of Schick Test Dose	24 Hr.	48 Hr.	72 Hr.	96 Hr.
Before vitamin C	— 10 —	* 15 *	* 20 *	* 20 *
After vitamin C	0	— 15 —	* 20 × 15 *	* 20 *

TABLE 2.—*Case 3*

	Diameter of Reaction to Schick Test After			
Injection of Schick Test Dose	24 Hr.	48 Hr.	72 Hr.	96 Hr.
Before vitamin C	— 10 —	* 12 *	+ 15 +	+ 15 +
After vitamin C	* 15 *	+ 15 +	+ 15 +	+ 15 +

TABLE 3.—*Case 4*

	Diameter of Reaction to Schick Test After		
Injection of Schick Test Dose	24 Hr.	48 Hr.	72 Hr.
Before vitamin C	* 15 *	+ 20 +	+ 20 +
½ hour after	* 15 *	+ 20 +	+ 20 +
1 hour after	* 15 *	* 20 *	+ 20 +
2 hours after	* 10 *	+ 10 +	+ 10 +
3 hours after	* 12 *	+ 15 +	+ 15 +
12 hours after	* 15 *	+ 24 +	+ 20 +

CASE 4.—C. A., a boy 3 years of age, received intramuscularly 600 mg. of cevitamic acid in the form of its sodium salt. Schick tests were then done at varying intervals, as indicated in table 3.

In this case there appeared to be a slight diminution in the size of the reactions after the two hour and the three hour interval (fig. 1). The reaction after the twelve hour interval, however, was slightly more pronounced than that before the administration of vitamin C.

In the cases reported hereafter, relatively larger doses of the vitamin were employed because of the possibility that the previously administered doses had been insufficient for our purpose.

CASE 5.—E. C., a girl 1½ years of age, received intravenously 300 mg. of cevitamic acid in the form of its sodium salt. Schick tests were then done at intervals, as shown in table 4.

A slight diminution in the intensity appeared in the last three reactions, namely, those to the one and one-half hour, the three hour and the six hour injection.

CASE 6.—J. G., a boy 1 year of age, received 450 mg. of cevitamic acid intravenously, and 350 mg. intramuscularly, in the form of its sodium salt. Schick tests were then performed after varying intervals, as indicated in table 5. The vitamin C appeared to have no effect. Rather the reaction to the Schick test given prior to the administration of the vitamin was slightly smaller and less intense than the reactions following the administration of the cevitamic acid.

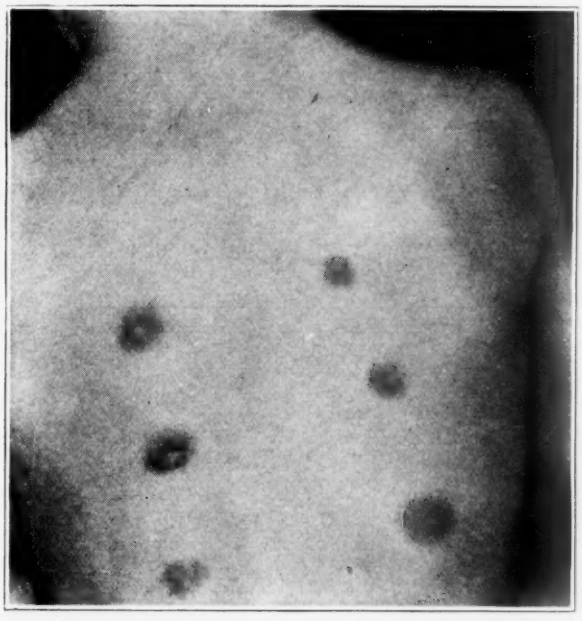

Fig. 1 (case 4).—This 3 year old child received 600 mg. of cevitamic acid intramuscularly in the form of its sodium salt. A Schick test dose had previously been injected in the left upper part of the back. After the administration of the vitamin, Schick test doses were injected at intervals of one-half, one, two, three and twelve hours. These injections were given in order from above down, left and then right. This photograph was taken approximately forty-eight hours after the injections.

CASE 7.—J. A., a girl 9 years of age, was given intravenously 475 mg. of cevitamic acid in the form of its sodium salt. Schick tests were then done at varying intervals, as shown in table 6.

No significant alteration of the reactions was present.

CASE 8.—L. S., a boy 6 years of age, received intravenously 1,000 mg. of cevitamic acid in the form of its sodium salt. In this case a huge dose was intravenously given without effect.

Case 9.—A. O'C., a boy 9 years of age, received intravenously 1,100 milligrams of cevitamic acid in the form of its sodium salt. Again a large dose of cevitamic acid was employed without demonstrable effect.

Table 4.—*Case 5*

Injection of Schick Test Dose	Diameter of Reaction to Schick Test After				
	24 Hr.	48 Hr.	72 Hr.	96 Hr.	120 Hr.
Before vitamin C	— 10 —	— 10 *	* 13 × 10 *	* 10 *	* 10 *
¼ hour after	— 10 —	* 12 *	* 12 × 10 *	* 15 × 10 *	* 10 *
½ hour after	— 10 —	— 15 × 10 *	* 14 × 10 *	* 15 × 10 *	* 10 *
1½ hours after	— 5 —	* 10 *	— 10 —	— 10 —	— 10 —
3 hours after	— 10 —	* 15 —	— 10 × 15 —	— 10 × 15 —	— 10 —
6 hours after	— 10 —	* 15 × 10 —	— 10 × 15 —	— 10 —	— 10 —

Table 5.—*Case 6*

Injection of Schick Test Dose	Diameter of Reaction to Schick Test After	
	24 Hr.	48 Hr.
Before vitamin C	— 10 —	— 10 —
½ hour after	— 15 —	* 15 *
1 hour after	— 10 —	* 15 *
1½ hours after	— 10 —	* 20 *
2 hours after	— 15 —	* 14 *
3 hours after	— 15 —	* 15 *
5 hours after	— 15 —	* 15 *
6 hours after	— 10 —	* 15 *

Table 6.—*Case 7*

Injection of Schick Test Dose	Diameter of Reaction to Schick Test After			
	24 Hr.	48 Hr.	72 Hr.	96 Hr.
Before vitamin C	— 10 —	* 10 *	* 10 *	* 20 *
¼ hour after	— 10 —	— 10 —	— 10 —	* 15 *
½ hour after	0	— 10 —	— 10 —	* 20 *
1 hour after	0	— 15 —	— 15 —	* 25 *
2 hours after	— 10 —	— 10 —	— 10 —	— 10 —
3½ hours after	— 10 —	* 12 *	— 12 *	* 20 × 15 *
6 hours after	— 10 —	— 10 —	— 10 —	* 20 × 15 *

Table 7.—*Case 8*

Injection of Schick Test Dose	Diameter of Reaction to Schick Test After	
	24 Hr.	48 Hr.
Before vitamin C	— 15 —	* 20 *
½ hour after	— 15 —	* 20 —
1½ hours after	— 15 —	+ 20 +
3 hours after	— 12 —	+ 15 +

Vitamin C, even in large amounts, given intravenously did not seem to influence the reaction to the Schick test, possibly because the intravenous mode resulted in too rapid excretion, insufficient local deposition at the site of the test or a combination of both factors. We therefore studied the effect of the local administration of vitamin C on the reaction to the Schick test.

CASE 10.—M. B., a boy 9 years of age, was given 75 mg. of cevitamic acid in the form of its sodium salt locally, i. e., subcutaneously on the flexor surface of the upper part of the right arm. From ten to fifteen minutes later a Schick test was done at the site of the injection of vitamin, and another Schick test was done low on the forearm, serving as a control.

TABLE 8.—*Case 9*

Injection of Schick Test Dose	Diameter of Reaction to Schick Test After		
	24 Hr.	48 Hr.	72 Hr.
Before vitamin C	* 20 × 25 *	* 20 *	— 15 —
½ hour after	* 15 × 30 *	* 20 *	— 12 —
2½ hours after	* 20 *	* 20 *	— 15 —

TABLE 9.—*Case 10*

Injection of Schick Test Dose	Diameter of Reaction to Schick Test After			
	24 Hr.	48 Hr.	72 Hr.	96 Hr.
Before vitamin C	— 15 —	— 18 —	* 20 *	* 20 *
At site of injection of vitamin C	— 15 —	— 20 —	* 20 *	+ 20 +
Away from site of injection of vitamin C	— 15 —	— 19 —	* 20 *	+ 20 +

TABLE 10.—*Case 11*

	Diameter of Reaction to Schick Test After			
	24 Hr.	48 Hr.	72 Hr.	96 Hr.
Schick test, 0.1 cc. intracutaneously	0	— 10 —	— 10 —	— 10 —
Schick control, 0.1 cc. intracutaneously	0	0	0	0
50 mg. of vitamin C intracutaneously followed in 5 minutes by a Schick test at the same site	— 20 —	— 15 × 20 —	— 20 —	— 15 —
50 mg. of vitamin C subcutaneously followed in 5 minutes by a Schick test at the same site	— 20 —	— 20 —	— 30 × 20 —	— 20 —
1 cc. of physiologic solution of sodium chloride intracutaneously followed in 5 minutes by a Schick test at the same site	— 15 —	— 15 × 10 —	— 20 —	— 13 —
50 mg. of vitamin C mixed with 0.1 cc. of diphtheria toxin for 30 minutes at room temperature, and then injected intracutaneously	— 30 —	— 10 —	0	0
1 cc. of physiologic solution of sodium chloride mixed with 0.1 cc. of diphtheria toxin for 30 minutes at room temperature and then injected intracutaneously	— 15 —	— 25 × 15 —	— 30 × 20 —	— 25 —

The results again failed to show any influence of the vitamin C on the reaction to the Schick test. Nevertheless, we continued to study the effects of local administration and in addition the effects of intravenous injection of in vitro mixtures of diphtheria toxin and vitamin C.

CASE 11.—R. B., a boy 7 years of age, received a series of seven tests, as outlined in table 10. In this case the only reaction which was appreciably diminished in intensity was that to the in vitro mixture of diphtheria toxin and vitamin C.

CASE 12.—J. R., a boy 2½ years of age, received ten tests, as outlined in table 11. On the whole, no significant effects were seen.

CASE 13.—F. L., a girl 4 years of age, received seven tests, as outlined in table 12. In this case we noted that the in vitro mixtures, including the saline control solution, caused reactions which were somewhat less elevated and less erythematous than the reaction to the original Schick test. However, the diameter of these reactions was considerably larger.

TABLE 11.—*Case 12*

	Diameter of Reaction to Schick Test After			
	24 Hr.	48 Hr.	72 Hr.	96 Hr.
Schick test, 0.1 cc. intracutaneously	0	— 12 —	— 13 —	* 13 *
Schick control, 0.1 cc.	0	0	0	0
25 mg. of vitamin C mixed with 0.1 cc. of diphtheria toxin, injected immediately	0	— 4 —	— 5 —	— 6 —
50 mg. of vitamin C mixed with 0.1 cc. of diphtheria toxin, injected immediately	0	— 7 —	— 30 × 20 —	— 30 × 20 —
75 mg. of vitamin C plus 0.1 cc. of diphtheria toxin, injected immediately	— 5 —	— 5 —	— 20 —	— 30 × 20 —
100 mg. of vitamin C plus 0.1 cc. of diphtheria toxin, injected immediately	— 5 —	— 5 —	— 30 × 20 —	— 30 × 20 —
50 mg. of vitamin C plus 0.1 cc. of diphtheria toxin, kept at room temperature 30 minutes and then injected intracutaneously	0	— 5 —	— 20 —	— 20 —
0.4 cc. of saline solution plus 0.1 cc. of diphtheria toxin, kept at room temperature 30 minutes and then injected intracutaneously	— 5 —	— 5 —	— 30 × 20 —	— 30 × 20 —
50 mg. of vitamin C plus 0.1 cc. of diphtheria toxin, kept at room temperature 2½ hours and then injected intracutaneously	0	— 15 —	— 10 —	— 10 —
0.4 cc. of saline solution plus 0.1 cc. of diphtheria toxin, kept at room temperature 2½ hours and then injected intracutaneously	0	— 12 —	— 20 —	— 15 —

TABLE 12.—*Case 13*

	Diameter of Reaction to Schick Test After			
	24 Hr.	48 Hr.	72 Hr.	96 Hr.
Schick test, 0.2 cc. intracutaneously	— 10 —	— 12 —	* 15 *	+ 10 +
Schick control, 0.2 cc intracutaneously	— 10 —	0	0	0
50 mg. of vitamin C mixed with 0.2 cc. of diphtheria toxin, injected after 5 minutes	* 10 *	— 10 —	— 10 —	— 10 —
100 mg. of vitamin C mixed with 0.2 cc. of diphtheria toxin, injected after 25 minutes	— 10 *	— 20 —	— 25 —	— 20 —
100 mg. of vitamin C mixed with 0.2 cc. of diphtheria toxin, injected after 20 minutes	— 10 —	— 20 —	— 25 —	— 20 —
100 mg. of vitamin C mixed with 0.2 cc. of diphtheria toxin, injected after 45 minutes	— 10 —	— 20 —	— 20 —	— 20 —
0.2 cc. of physiologic solution of sodium chloride mixed with 0.2 cc. of diphtheria toxin, injected after 45 minutes	— 5 —	— 15 —	— 12 —	— 10 —

CASE 14.—M. L., a girl 5 years of age, received five tests, as outlined in table 13. No striking alterations in the reactions were seen other than a slight diminution in the intensty, which was brought about even with the use of physiologic solution of sodium chloride. The diminution in intensity was more evident in the last test, in which an in vitro mixture which had been standing four hours at room temperature was injected

Shortly after the completion of our study, we found that Widenbauer and Saretz [27] had also attempted to ascertain the effect of vitamin C on the reaction to the Schick test. They found that if 0.2 cc. of diphtheria toxin was incubated with 50 mg. of cevitamic acid at 37 C. for from fifteen to thirty minutes and then injected into a person with a positive reaction to the Schick test, the reaction would be either weakly positive or negative. In vivo tests, in which the patient received cevitamic acid in large amounts by mouth affected the reaction to the Schick test in no way.

In reviewing our series of cases we concluded that no striking alteration of the reaction to the Schick test can be obtained by the use of vitamin C systemically, whether orally, intramuscularly or intravenously; nor can an alteration be obtained by local administration. The injection of in vitro mixtures of diphtheria toxin and vitamin C

TABLE 13.—*Case 14*

	Diameter of Reaction to Schick Test After			
	24 Hr.	48 Hr.	72 Hr.	96 Hr.
Schick test, 0.2 cc. intracutaneously	— 15 —	— 15 —	— 20 —	* 25 *
Schick control, 0.2 cc. intracutaneously	— 13 —	0	0	0
100 mg. of vitamin C intracutaneously followed by 0.2 cc. of diphtheria toxin at the same site	— 30 —	— 20 —	— 30 —	— 25 —
0.3 cc. of physiologic solution of sodium chloride intracutaneously followed by 0.2 cc. of diphtheria toxin at the same site	— 20 —	— 20 —	— 30 —	— 25 —
100 mg. of vitamin C mixed with 0.2 cc. of diphtheria toxin, injected after 4 hours	— 30 —	— 20 — (faint)	— 20 — (faint)	— 20 — (very faint)

seemed to result in reactions of slightly diminished intensity in some of our cases. This effect appeared more evident the longer the mixtures were allowed to remain in contact in vitro before being injected.

Since the greater part of the investigations concerning diphtheria toxin and vitamin C was carried on in vitro, and since most of the workers reported more successful results with neutralization in vitro than with that in vivo, one should certainly consider the chemical alterations which might occur in the in vitro mixtures. Roux and Yersin [3] showed that acids weakened the toxic action of the diphtheria toxin. The toxin was not destroyed but was changed into an atoxic modification by the addition of acid. Von Gröer [28] studied in great detail the influence of changes in p_H on the diphtheria toxin. From his work he concluded that diphtheria toxin may be considered an

27. Widenbauer, F., and Saretz, S.: Untersuchungen über die antitoxische Wirkung von Vitamin C auf diphtherietoxin am Menschen, Klin. Wchnschr. **15**: 1131-1132 (Aug. 8) 1936.

28. von Gröer, F.: Diphtherietoxinstudien: I. Ueber den Einfluss der Wasserstoffionenkonzentration auf das Diphtherietoxin, Biochem. Ztschr. **138**:13-34, 1923.

amphoteric electrolyte the toxic nature of which is bound up in its acid properties. The toxicity of the toxin is changed by the p_H. The optimum p_H was found to be between 8.5 and 9.2. The toxin was found ineffective at a p_H of 5 and at a p_H of 12. The graph reproduced from von Gröer's paper (fig. 2) represents the degree of toxicity of the toxin with the p_H at various levels. The curve resembles the dissociation curve of an amphoteric electrolyte. He expressed the opinion that to characterize the toxicity of the toxin properly one should give not only the *Giftwert* (number of minimal necrosing doses per cubic centimeter of toxin) but the p_H at which it was determined.

Many of the workers reporting results made no attempt to use neutralized cevitamic acid. It is well known that this substance is strongly acid. As was mentioned, diphtheria toxin becomes ineffective at a p_H of 5. Therefore, results obtained with unneutralized cevitamic

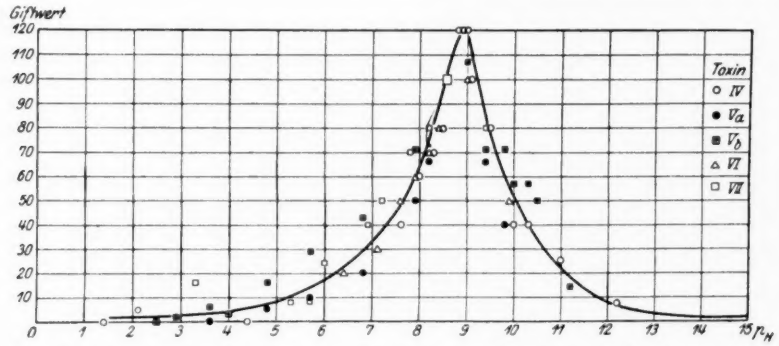

Fig. 2.—Curves showing the changes in the toxin titer of diphtheria toxin at various hydrogen ion concentrations. *Giftwert* is the number of minimal necrosing doses per cubic centimeter of toxin.

acid lose significance. Some investigators employed neutralized cevitamic acid (sodium salt of cevitamic acid) in their in vitro tests. We thought it of interest to determine the actual p_H values of neutralized cevitamic acid and diphtheria toxin both before and after mixing. Accordingly, we ascertained (by means of the glass electrode apparatus) the following p_H values.

	p_H
Diphtheria toxin for Schick test (preparation no. 68, lot no. 191)	7.90
Sodium salt of cevitamic acid, 0.111 mg. dissolved in 2 cc. of distilled water	6.75
Sodium salt of cevitamic acid, 0.111 mg. dissolved in 0.5 cc. of distilled water	6.65
Mixture of 0.2 cc. of diphtheria toxin and 0.111 mg. of sodium salt of cevitamic acid dissolved in 0.5 cc. of distilled water	6.70
Mixture of 0.2 cc. of diphtheria toxin and 0.111 mg. of sodium salt of cevitamic acid dissolved in 0.5 cc. of distilled water after standing 2 hours at 36 C.	6.50
Mixture of 0.2 cc. of diphtheria toxin and 0.111 mg. of sodium salt of cevitamic acid dissolved in 0.5 cc. of distilled water after standing 22 hours at room temperature (18-25 C.)	6.40

The p_H measurements were made at 19 C. unless otherwise specified. The precision was plus or minus 0.05 p_H unit or better.

From this tabulation is is apparent that even with the use of neutralized cevitamic acid there is a significant drop in the p_H values of the mixture. The drop increases the longer the mixture is allowed to stand. The effect of the change in the p_H may be sufficient to diminish the toxicity of the diphtheria toxin, so that it elicits a more weakly positive or even a negative reaction to the Schick test. The curve shown in figure 2 reveals the marked decrease in toxicity at the p_H values that were obtained for the mixtures. Since the toxin is supposedly not destroyed by the addition of acid but only changed into an atoxic modification, the readjustment of the p_H value by the proper addition of alkali should result in a renewed potency of the toxin. We are at the present time carrying out work which tends to confirm this supposition. The results will be published in a subsequent article.

Another characteristic of cevitamic acid must be borne in mind. It has been well established that this acid plays an important rôle in oxidation-reduction systems and is a powerful reducing agent.[1] This feature must be considered as a possible factor in the in vitro neutralization of diphtheria toxin.

One more property ascribed to vitamin C should be mentioned here. Much has been written concerning the "tightening" effect of the substance on the capillaries. According to some writers,[29] a decrease in capillary fragility occurs after the administration of vitamin C. If this is true, it is another possible explanation for reactions of lessened intensity. The diminution in reaction may be brought about by the effect on the capillaries locally at the site of the test, resulting in lessened exudation. Recently, Szent-Györgyi and his co-workers [30] ascribed the capillary effects to a new vitamin, P, which occurs with but is not related to vitamin C. This vitamin is a member of the flavonol group of vegetable dyes.

Reactions due to inactivation of toxin brought about by changes in p_H or by processes of oxidation and reduction are classed as nonspecific. In short, vitamin C does not come under the category of a true antitoxin. It does not conform to the criteria outlined by Schick, von Gröer and Kassowitz.[10]

---

29. (*a*) Dalldorf, G., and Russell, H.: Effect of Vitamin C Injections on Capillary Resistance, J. A. M. A. **104**:1701-1702 (May 11) 1935. (*b*) Sedlacek, E.: Stillung kapillarer Blutungen durch Cebion, Med. Klin. **31**:848-849 (June 28) 1935.

30. Armentano, L.; Bentsáth, A.; Béres, T.; Rusznyák, S., and Szent-Györgyi, A.: Ueber den Einfluss von Substanzen der Flavongruppe auf die Permeabilität der Kapillaren, Vitamin P, Deutsche med. Wchnschr. **62**:1325-1328 (Aug. 14) 1936.

SUMMARY

The literature concerning the relation of vitamin C to diphtheria toxin is surveyed.

The influence of vitamin C on diphtheria toxin was studied in a series of children who were known to react positively to the Schick test by means of Schick tests done at varying intervals after the administration of cevitamic acid. All modes of administration—oral, intravenous, intramuscular, subcutaneous and intracutaneous—were tried. With all, the vitamin C was found to be ineffective if one judged by the persistence of undiminished positive reactions to the Schick test even after doses as high as 1,100 mg. were given intravenously.

A slight neutralizing effect of vitamin C was noted when it was mixed with diphtheria toxin in vitro and then injected intracutaneously. This effect was more apparent the longer the mixture was allowed to stand.

The neutralizing effects of vitamin C are probably due to nonspecific inactivation brought about by changes in the p_H or by alterations due to changes made by the acid in the oxidation-reduction system or to both factors.

The possibility of a capillary effect due to vitamin C is mentioned.

Hoffmann-La Roche, Inc., supplied the cevitamic acid for these experiments. Prof. W. C. MacTavish, chairman of the chemistry department of Washington Square College, New York University, cooperated in the p_H determinations.

The cases for this study were from the pediatric service of Dr. Béla Schick, of the Mount Sinai Hospital, and from the Willard Parker Hospital.

Dr. G. Shwartzman and Dr. A. L. Bachman, of the Mount Sinai Hospital, gave assistance and constructive criticism.

A METABOLIC STUDY OF FIVE CHILDREN WITH THE NEPHROTIC SYNDROME

I. A REPORT ON CERTAIN CONSTITUENTS OF THE BLOOD, THE BASAL METABOLISM AND THE ENERGY EXCHANGE

A. GRAEME MITCHELL, M.D.

CLARE R. RITTERSHOFER, M.D.

CHI CHE WANG, PH.D.

MILDRED KAUCHER, M.S.

MARY WING, M.S.

AND

CORINNE HOGDEN, M.S.

CINCINNATI

Metabolic studies have been conducted on five children who presented the symptoms usually described as typical of lipoid nephrosis. The age of the patient, the sex and the number of days under observation in each case are listed in table 1.

TABLE 1

Case	Patient	Sex	Age in Years	No. Days of Observation
1	T. D.	Male	3	147
2	L. B.	Female	3	54
3	J. M.	Male	4	229
4	E. L.	Female	11	51
5	D. E.	Female	16	255

The nephrotic syndrome was complicated by the presence of hematuria in one child (case 4) and by hypertension in another (case 5). The last-mentioned patient when first seen was markedly undernourished and weak and had been confined to bed for six months; the other four appeared to be in good physical condition, except for the symptoms associated with the condition under discussion.

GENERAL PROCEDURE

The five children were admitted to the metabolic unit of the Children's Hospital, which has been previously described.[1] There they were constantly attended by

From the Children's Hospital Research Foundation, and the Department of Pediatrics, University of Cincinnati, College of Medicine.

1. Wang, C. C.; Kaucher, M., and Wing, M.: Metabolism of Adolescent Girls: I. Basal Metabolism and Energy Exchange, Am. J. Dis. Child. **51**:801 (April) 1936.

specially trained nurses. During the period of each observation the children were weighed each morning at the same hour and measured each week. Their food was prepared in the diet kitchen of the unit and weighed daily. The composition of the food was calculated according to standard tables.[2] Each experimental period consisted of at least two consecutive periods of three days each, preceded by a preliminary period of a minimum of five days. During the experimental periods basal metabolism was determined, and foods, feces and urine were analyzed for nitrogen, energy value, total solids and minerals, including calcium, phosphorus, sodium, magnesium and potassium. The amounts of creatine and creatinine in the urine and of fat in the food and the feces were determined. With the exception of determinations of the urinary nitrogen and albumin for two patients (cases 5 and 3), these chemical analyses were made only during experimental periods. The albumin nitrogen of the urine was calculated from the difference between the total nitrogen, determined by the macro-Kjeldahl method, and the nitrogen of the urine after removal of the albumin determined by treating with an equal volume of 10 per cent trichloro-acetic acid. The value of the albumin in the urine was obtained by multiplying the amount of albumin nitrogen by the factor 6.25. At convenient times red blood cell counts were made, and samples of blood were analyzed for total serum protein, serum albumin, serum nonprotein nitrogen, cholesterol and hemoglobin. This paper is concerned only with the clinical data, the results of studies of the blood, the basal metabolism and the energy exchange of the five patients.

CLINICAL FINDINGS AND EFFECT OF TREATMENT

Case 1.—A boy 2 years and 8 months of age was transferred from the Cincinnati General Hospital. He had been in that institution for four days. Physical examination revealed marked edema of the arms, the eyelids and the lower parts of the legs and the presence of fluid in the abdomen. His skin was pale and moist and had a peculiar waxy appearance. There were old healed impetiginous lesions on his hands and feet. His temperature was 100 F., and his blood pressure was normal. The daily record of this boy is given in chart 1. He was placed on a diet high in proteins and poor in salt (i. e., with no added salt), and he received no medication. He lost fluid rapidly and within a week was almost free from edema, except for a certain amount of ascites. In spite of the diet, the edema reappeared in a few days and became so pronounced that it was deemed wise to resort to medication. The dosages of ammonium chloride, potassium chloride, salyrgan and dextrose are indicated in chart 1. Salyrgan was administered intravenously. At first ammonium chloride was given daily in 1 Gm. doses, and later it was administered in combination with 2 Gm. of potassium chloride. There was a slight temporary improvement in the patient's edematous condition. During two months (November and December, chart 1) he had several infections of the respiratory tract and for most of this time had a slightly elevated temperature. On December 12 examination showed a small amount of fluid at the base of the left lung. From this date to the end of the month his condition was generally unsatisfactory, and occasionally he felt nauseated and at times vomited. Bronchitis then developed (temperature 104.4 F.), and he was transferred to the general medical service, where he received a regular hospital diet and all medication by mouth was stopped. Pitting edema of the lower extremities

2. Bradley, A. V.: Tables of Food Values, Peoria, Ill., Manual Arts Press, 1931.

and ascites were still present. Ammonium chloride, 1 Gm. daily, was used again. Within a week the patient's general condition improved, and he lost considerable edema. On recovery from tonsillectomy and adenoidectomy, performed under general anesthesia, all noticeable edema disappeared. After return to the metabolic unit he received the same diet and no medication. His edema returned in about ten days and persisted throughout the period of observation. He was removed from the hospital against advice, while there was still edema around his eyes and in his lower extremities.

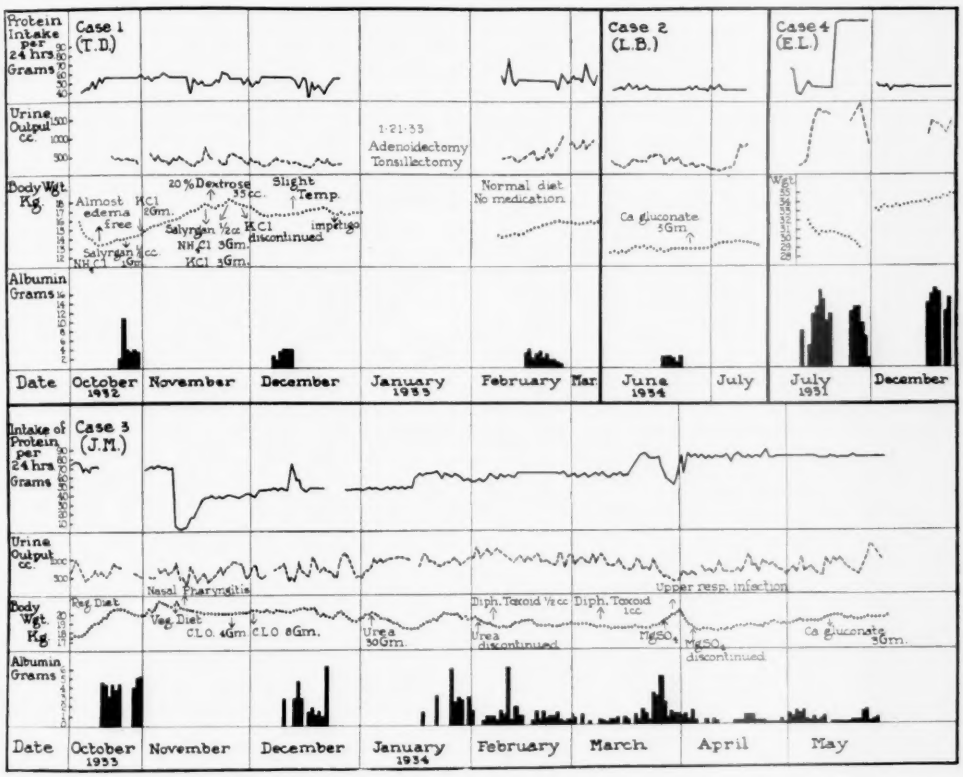

Chart 1.—Daily records of intake of protein, body weight and output of urine and albumin in four cases of nephrosis.

CASE 2.—A girl 3 years of age had been observed in the Children's Hospital from time to time over a period of seven months with a condition diagnosed as nephrosis, in some exacerbations of which she had been gravely ill. She had been given acacia, and on several occasions abdominal paracentesis had been performed. A diet high in protein and poor in salt and various diuretics had been tried, but there had been only temporary improvement. For the first twenty-five days she was in the metabolic unit she received diet low in salt and high in protein (3.5 Gm. per kilogram). No medication was given. Later 3 Gm. of calcium gluconate was administered with this diet. Her condition remained practically unchanged during the period of observation.

CASE 3.—A boy 4 years and 3 months of age was transferred to the metabolic unit from the medical service of the hospital with a diagnosis of nephrosis. Symptoms of this condition had been noted eight months earlier. His acute illness began with generalized edema two weeks prior to hospitalization. He had been treated with a high protein diet and with magnesium sulfate.

Physical examination showed a pale child with edema of the face, abdomen and extremities. His blood pressure was normal. He received a regular diet for about one month, during which time his edema increased. He was then placed on a modified Schiff diet,[3] consisting of fresh fruits and vegetables. Unfortunately, the child disliked vegetables and failed to eat enough to meet his requirements in proteins and calories. There was a steady increase of edema, and it was considered advisable after four days to add to this diet 22 Gm. of egg yolk and 200 Gm. of milk. These amounts of egg yolk and of milk were increased to 75 and 600 Gm., respectively. The intake of proteins for the entire period is shown in chart 1. The medication he received during the study is recorded on his weight curve (chart 1). For a period of one week magnesium sulfate was given, starting on March 28, as indicated in the chart. The amounts of magnesium sulfate administered on successive days were 11, 20, 33, 40, 41, 40 and 42 Gm. Calcium gluconate, 3 Gm. daily, was given by mouth for another period of two weeks. From time to time complications, such as recurrent abdominal pain, infection of the upper part of the respiratory tract, mild furunculosis, and otitis media, developed.

Edema developed in recurring waves during the period of observation, and it was therefore difficult to determine whether temporary improvement was the result of any one medication. It is certain, however, that no medication used produced definite and prolonged reduction of the edema. When the boy was discharged from the hospital at the request of his mother, he was in fair condition and practically free from edema, except for a small amount of ascites.

CASE 4.—A girl 11 years and 4 months of age was transferred from the Cincinnati General Hospital with symptoms of nephrosis accompanied with a complicating hematuria. The onset of her illness, when edema was first noticed, had been three years previously. Since that time there had been repeated remissions and exacerbations of the edema. Thyroid extract and ammonium chloride had been used at various times, but little apparent effect had followed.

Physical examination showed a pale girl with marked generalized edema. In addition to albuminuria and oliguria, hematuria was discovered. The blood pressure was normal. The patient was given a salt-poor diet with 2 Gm. of protein per kilogram, the protein being gradually increased to 4 Gm. per kilogram, as shown in chart 1. Her condition remained unchanged. After part of this study was completed, she was returned to the Cincinnati General Hospital.

When she was received in December for further observation, the clinical picture was similar to that observed at the time of the previous admission. For three weeks she was placed on a daily diet containing 1.5 Gm. of protein per kilogram. No medication was employed at any time. It was planned to increase the intake of protein gradually and to continue the studies. Unfortunately, on January 1 the patient became acutely ill, with pain and tenderness over both kidneys, and she was immediately transferred to the medical service. Her condition became steadily worse, and she died on January 13. Necropsy showed lipoid nephrosis, complicated with chronic diffuse interstitial nephritis, chronic myocarditis and syphilitic aortitis.

---

3. Schiff, E.: Ueber die Lipoidnephrose im Kindesalter, Ernährungstherapie und einige klinische Beobachtungen, Jahrb. f. Kinderh. **137**:1, 1932.

CASE 5.—A girl 15 years and 8 months of age was transferred from the Cincinnati General Hospital, where, under observation for four months, her condition had been diagnosed as chronic diffuse glomerular nephritis associated with lipoid nephrosis. During her hospitalization at that institution she had received a high protein, salt-poor diet; thyroid extract and various diuretics, including potassium chloride and ammonium nitrate. Thoracentesis of the left side of the chest had been performed several times.

On admission she was greatly malnourished and weak and presented generalized edema. She was 20 per cent underweight, according to the standard of Baldwin

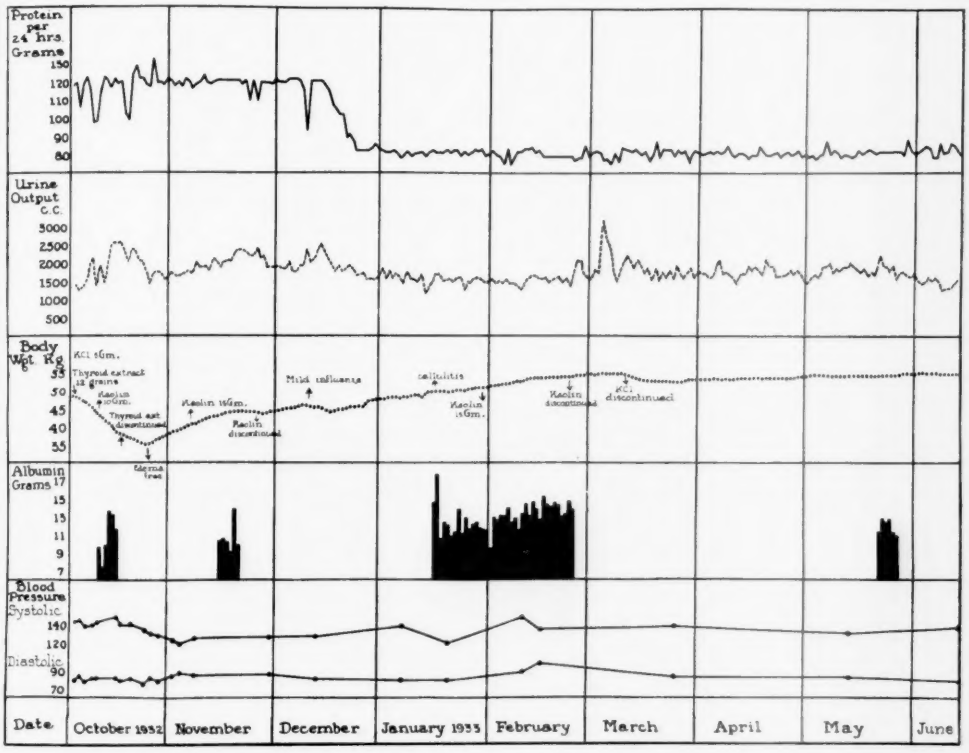

Chart 2.—Daily records of body weight, intake of proteins and output of urine and albumin in case 5 (D. E.).

and Wood. The blood pressure was 148 systolic and 85 diastolic. A systolic murmur was heard over the pulmonic area. During the first two weeks she was kept on the diet and treatment that she had been receiving at the time of admission, that is, a diet of 122 Gm. of protein, 12 grains of thyroid extract and 5 Gm. of potassium chloride daily (chart 2). Her edema decreased steadily after admission, and on October 18 (see chart 2, body weight curve) the edema of her ankles had almost disappeared and fluid was no longer demonstrable in her abdomen. At this time she was 34 per cent underweight. The fluid in the left side of her chest was still present. After this period marked edema never developed, and the patient gained flesh steadily. Shortly she was able to get about,

attend school in the hospital and work in the department of occupational therapy. Her daily intake of protein was lowered to 80 Gm., as shown in chart 2, and she was kept at this level for five and a half months. After that time she was discharged, her weight being normal and the edema slight. During her stay she had several infections of various types, but none of them resulted in the reappearance of pronounced edema. Medication administered is indicated along the body weight curve of chart 2.

It is obvious that cases 1 and 5 are not exactly comparable. The patients were studied simultaneously, were both placed on the same type of diet and both began to lose their edema immediately. In case 1

TABLE 2.—*Results of Studies of the Blood*

Case	Date	Serum Protein, Gm. per 100 Cc.	Serum Albumin, Gm. per 100 Cc.	Serum Globulin, Gm. per 100 Cc.	Albumin-Globulin Ratio	Serum Nonprotein Nitrogen, Mg. per 100 Cc.	Cell Volume, Vol. %	Red Cell Count	Hemoglobin, Gm. per 100 Cc.	Cholesterol Content, Mg. per 100 Cc.
1	10/10/32	3.53	0.92	2.61	0.35	29	....	.....	....	320
	11/18/32	3.67	0.94	2.73	0.34	18	36.0	3,780,000	13.1	580
	2/13/33	3.90	2.01	1.89	1.06	18	30.8	3,810,000	10.0	435
2	11/27/33	3.60	0.96	2.70	0.36	19	....	3,800,000		
	3/19/34	2.68	0.75	1.93	0.39	23	....	4,400,000	....	185
	7/31/34	3.58	....	....	....	25				
	9/10/34	3.54	0.52	3.02	0.17	30				
3	8/ 8/33	4.50	1.70	2.80	0.60	32	....	.....	....	527
	10/ 6/33	3.98	1.30	2.68	0.49	25	....	.....	....	444
	11/ 8/33	3.49	0.62	2.87	0.22	26	37.7	4,240,000	13.8	544
	1/15/34	4.48	0.73	3.75	0.19	32	39.9	4,390,000	12.8	624
	5/ 8/34	4.40	1.70	2.70	0.63	29	40.9	4,670,000	14.3	357
	5/28/34	4.01	1.53	2.48	0.62	23	....	.....	....	435
4	7/25/31	4.47								
	7/28/31	3.75	1.34	2.41	0.50	..	....	.....	....	266
	7/31/31	3.73	1.32	2.41	0.55					
	8/24/31	3.74	1.34	2.40	0.56	..	....	.....	....	266
	1/ 1/32	5.05	....	....	....	73	....	2,400,000		
5	9/ 6/32	2.33	0.97	1.36	0.71	71				
	10/ 7/32	3.03	1.45	1.58	0.92	65				
	10/18/32	3.42	1.52	1.90	0.80	50				
	11/28/32	3.66	1.86	1.80	1.03	36	31.3	3,430,000	11.3	485
	1/ 3/33	....	....	....	....	..	31.2	3,680,000	11.0	470
	1/23/33	2.90	1.78	1.12	1.59	38	30.0	3,270,000	11.2	477
	6/ 1/33	4.64	2.70	1.94	1.42	46	....	.....	....	351
	4/14/34	5.26	2.76	2.50	1.10	45	....	4,080,000	11.8	303

the improvement lasted only one week, whereas in case 5, even though administration of thyroid extract was discontinued, generalized edema never reappeared. It would appear that the long-continued absence of edema in the latter case was due, not entirely to the diet or the medication, but rather to the fact that there was a progressing nephritic condition and that the nephrotic syndrome was disappearing. This is suggested by the rise in the protein content of the serum, the reduction of cholesterol in the blood and the increase in the concentration of the nonprotein nitrogen constituents of the blood serum (table 2).

In general, the studies on the patients having the uncomplicated nephrotic syndrome indicated that diet, diuretics and medication have no prolonged or marked effect on the edematous state.

EXCRETION OF URINARY PROTEIN

The volume of urine and the output of albumin of the patients are given in charts 1 and 2. The urine of all the patients contained albumin on admission, and with one exception (case 3) this condition persisted markedly throughout the entire study. It is evident from the charts that the intake of protein had little apparent effect on the output of albumin.

STUDIES OF THE BLOOD

In table 2 are collected studies of the blood of these patients. The findings confirm the presence of the nephrotic syndrome. In all cases the protein partition demonstrated the low total serum protein and the lowered ratio of albumin to globulin which are typical of the results obtained by all investigators of this condition. In every case and practically for the entire periods that these patients were under observation, the total serum protein was below the so-called edema level of 5 Gm. per hundred cubic centimeters (Linder, Lundsgaard and Van Slyke [4] and Moore and Van Slyke [5]). In spite of this, these patients were at times markedly improved and practically free from edema—an observation concurred in by a number of authors.[6] It appears impossible, then, to explain edema solely on the basis of a balance between colloidal osmotic pressure of the plasma and capillary blood pressure. Other factors which may play rôles have been suggested, such as colloidal osmotic pressure of fluids in the tissues, flow of lymph, mechanical pressure in the spaces in the tissues, permeability of the capillary walls, shift of electrolytes, existence of a hormonal influence, secretion of toxic agents and action of electrical forces.

The values for albumin in the serum of the five children were generally far below normal and variable. Although the number of subjects studied was small, we felt that the concentrations of albumin appeared to be correlated more closely with the state of edema than

4. Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: The Concentration of the Plasma Proteins in Nephritis, J. Exper. Med. **39**:887 (June) 1924.

5. Moore, N. S., and Van Slyke, D. D.: The Relationship Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, J. Clin. Investigation **8**:337 (April) 1930.

6. (*a*) Wordley, E.: The Effect of High Protein Diet on Albuminuria and Blood Urea in Cases of Nephritis, Quart. J. Med. **14**:88 (Oct.) 1920. (*b*) Cowie, D. M.; Jarvis, K. M., and Cooperstock, M.: Metabolism Studies in Nephrosis, with Special Reference to Relationship of Protein Intake to Nitrogen Retention, Edema and Albuminuria, Am. J. Dis. Child. **40**:465 (Sept.) 1930. (*c*) Calvin, J. K., and Goldberg, A. H.: Plasma Proteins and Edema: Their Relationship in a Group of Children Presenting the Nephrotic Syndrome, ibid. **42**:314 (Aug.) 1931.

did those of the total protein. In this we were in agreement with the findings of Barker and Kirk [7] and of Calvin and Goldberg.[6c]

The variations in the concentration of serum globulin were not as great as the changes in the concentrations of albumins. The factors that caused changes in the concentration of globulin are still not characterized definitely; therefore it is not possible to determine the significance of small changes in the ratio of albumin to globulin. In general, it may be stated that in the three typical cases, in which there was only a nephrotic syndrome, there was a marked reversal of the albumin-globulin ratio. Although in E. L. (case 4) the lipoid nephrosis was complicated at the terminal stage with chronic nephritis and increased nitrogenous retention, protein partitions obtained earlier show the typical reversal of the albumin-globulin ratio. This marked reversal never appeared in D. E. (case 5), and in general changes in her total protein were accompanied by corresponding changes in the concentration of albumin. This patient presented a complicated clinical picture. At times it was thought that her diet had much to do with the rise in the total protein content of her serum, her nutritional state and her improved clinical condition. It is probable too that in T. D. (case 1) the clinical improvement might be attributed, in part, to the diet.

In three cases repeated determinations of nonprotein nitrogen gave results within normal limits. In case 5 and in the one determination made during the terminal stage in case 4, the nonprotein nitrogen was elevated.

The values for cholesterol in the blood were markedly higher than normal. In D. E. (case 5), as the concentration of serum protein increased, the cholesterol content of the blood had a tendency to decrease.

The values for cell counts and for the concentration of hemoglobin showed that all five of the patients were only slightly anemic, and no definite changes were observed during the study.

BASAL METABOLISM; METHOD AND RESULTS

In 1917 Aub and DuBois [8] reported basal metabolism as low as from —27 to —40 per cent in patients suffering from "chronic parenchymatous nephritis" with edema. The lowest values were obtained for the patients with the most pronounced edema. These investigators stated that the decrease pointed to some cause other than mere dilution of tissue with inert fluid and distention of skin. Later Epstein and

7. Barker, M. H., and Kirk, D. J.: Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, Arch. Int. Med. **45**:319 (March) 1930.

8. Aub, J. C., and DuBois, E. F.: Clinical Calorimetry: XXII. The Respiratory Metabolism in Nephritis, Arch. Int. Med. **19**:865 (May) 1917.

Lande [9] noted that 60 per cent of nephrotic patients exhibited a basal metabolism between —10 and —22 per cent. Since then numerous scattered reports have appeared in the literature concerning the basal metabolism in nephrosis, the majority of which show values lower than normal.

The basal metabolism was determined for four of our five patients. At least three duplicate determinations were made on three consecutive mornings after one or more preliminary tests during each experimental period. The average of the two lowest results agreeing within 4 per cent is the figure reported in table 3. The method of Higgins and Bates [10] was followed, and the test was made while the child was asleep in all cases except that of D. E. (case 5). The method used for her has already been described.[1]

In table 3 the heat production of each of the four nephrotic patients is expressed in total calories per twenty-four hours, calories per kilogram and per centimeter per twenty-four hours, and calories per square meter per hour. With the exception of the first period of J. M. (case 3) and that of D. E. (case 5), during which time D. E. was receiving 12 grains of thyroid extract daily, the metabolism increased gradually during the entire period of observation. In L. B. (case 2) and J. M. (case 3) there was augmentation, regardless of the method of calculating calories, more marked in the former than in the latter patient. Since thyroid extract was not given to either of these patients, the increase could be attributed to changes in physical condition or, more probably, to growth. D. E. (case 5) showed an increase in heat production of over 10 per cent during the six and a half months, due, no doubt, to greater muscular development. Because of a rapid gain in body weight, her basal metabolism, expressed on the basis of either weight or surface area, decreased during the period.

The heat production of all four patients was compared with three of the available standards: of Benedict and Talbot, of Dreyer and of Harris and Benedict. The first is known to be especially suitable for children, while the other two have been considered more applicable to adults. The values for the basal metabolism of all four patients were within normal limits, according to the Benedict-Talbot standard. With the exception of D. E. (case 5), whose metabolism was within normal limits irrespective of the choice of standards, the heat production of all patients was from 15 to 30 per cent below the Dreyer standard. The

9. Epstein, A. A., and Lande, H.: Studies on Blood Lipoids: 1. The Relation of Cholesterol and Protein Deficiency to Basal Metabolism, Arch. Int. Med. **30**:563 (Nov.) 1922.

10. Higgins, H. L., and Bates, V.: New Method for the Determination of the Basal Metabolism of Babies and of Small Children, Am. J. Dis. Child. **39**:71 (Jan.) 1930.

TABLE 3.—*Basal Metabolism of Nephrotic Children*

Patient	Date	Age Yr.	Age Mo.	Sex	Height, Cm.	Weight Observed, Kg.	Weight Deviation from Baldwin, Wood Standard, per Cent	Surface Area, Sq. M.	Pulse	Respiratory Quotient	Calories per Twenty-Four Hours Total	Per Kg.	Per Cm.	Deviation from Standards B.-T. Referred to Weight, Percentage	Deviation from Standards Dreyer Referred to Age and Weight, Percentage	Deviation from Standards H.-B. Referred to Age, Weight and Height, Percentage	Calories per Sq. M. per Hour
Case 1, T. D.....	2/23-24/32	2	11	M	92.5	16.24	+18.7	0.686	128	0.823	823	50.7	8.8	+ 8.0	—24.1	+11.0	50.0
Case 2, L. B.....	6/ 8-13/34	3	0	F	85.5	13.25	+ 9.6	0.599	111	0.851	692	52.2	8.1	+ 6.9	—24.8	—25.3	48.2
	7/ 4- 5/34	3	1		86.1	13.86	+13.7	0.617	122	0.854	766	55.3	8.9	+10.9	—15.1	—17.9	51.7
Average.....	.....	.....		..	85.8	13.56	+11.7	0.608	117	0.853	729	53.8	8.5	+ 8.9	—20.0	—21.6	50.0
Case 3, J. M.....	11/ 4- 8/33	4	3	M	106.4	20.96	+22.6	0.837	102	0.843	836	39.9	7.9	— 7.5	—29.5	— 2.8	41.7
	1/ 7- 8/34	4	5		107.0	19.45	+12.4	0.785	90	0.830	802	41.3	7.5	— 5.0	—29.9	— 4.9	42.6
	2/22-3/3/34	4	7		107.3	18.87	+ 8.4	0.766	89	0.858	861	45.7	8.0	+ 4.1	—24.0	+ 3.3	46.8
	5/10-12/34	4	9		107.4	19.42	+11.6	0.784	98	0.828	887	45.7	8.3	+ 5.3	—20.0	+ 5.9	47.0
Average.....	.....	.....		..	107.0	19.68	+13.8	0.793	95	0.840	847	43.2	7.9	— 0.8	—25.9	+ 0.4	44.5
Av. of 4 normal..	.....	5	0	2M-2F	100.0	15.6	.....	0.667	89	0.840	887	55.0	8.8	+20.2	— 6.0	— 8.8	55.0
Case 5, D. E.....	10/11-12/32	15	8	F	164.6	43.84	—19.7	1.449	106	0.788	1,511	34.5	9.2	+22.1	+17.4	+15.7	43.5
	11/21-22/32	15	9		164.6	44.57	—19.7	1.459	74	0.930	1,228	27.6	7.5	— 0.9	— 5.4	— 6.4	35.1
	1/24-26/33	16	0		164.6	50.54	— 9.0	1.540	94	0.895	1,370	27.1	8.4	+ 8.8	— 0.7	— 0.1	37.1
	2/21-24/33	16	1		164.6	54.30	— 2.2	1.587	86	0.882	1,363	25.2	8.3	+ 7.2	— 5.6	— 2.9	35.8
	6/ 5- 6/33	16	4		164.6	55.46	— 0.1	1.599	84	0.830	1,398	25.3	8.5	+ 9.7	— 3.3	— 1.3	36.5
Average.....	.....	.....		..	164.6	49.74	—10.1	1.527	85*	0.865	1,340*	26.3*	8.2*	+ 6.2*	— 3.8*	— 2.7*	36.1*
Av. of 3 normal..	.....	16	0	F	158.3	48.49	.....	1.471	76	0.846	1,272	26.4	8.1	+ 1.8	— 6.1	— 4.9	36.1

* First period not included.

metabolism of all patients except L. B. (case 2) was within the normal range when compared with the Harris-Benedict standard. At two test periods the values obtained for L. B. (case 2) averaged 21.6 per cent below this standard.

Owing to the marked difference in the various standards, the basal metabolism of J. M. (case 3) and of D. E. (case 5) has been compared with the values obtained previously by us for apparently normal children of their respective ages. The basal metabolism of D. E. (case 5) was higher in every respect than the average of values obtained for three normal girls of her age but was well within normal limits. J. M. (case 3) had an average total heat production 3.9 per cent below the average value for four normal children (see table 3). When the comparison was made on the basis of body weight, stature or surface area, the values for heat production were —21.4 per cent, —10.2 per cent and —19.1 per cent, respectively. This difference was undoubtedly due to the fact that J. M. was exceptionally large for his age. Consequently, his total heat production was comparable to that of a child of his age but not to that of one of his size. The fact that there have been so many contradictory reports concerning basal metabolism in nephrosis (especially in children) may be explained, in part, by the differences in the standards employed by the various investigators.

Epstein and Lande [9] and Liu and Chu [11] observed an inverse correlation between basal metabolism and the cholesterol content of the blood. In our patients, also, this inverse correlation apparently held. For example, the highest metabolism of J. M. (case 3) was accompanied by the lowest cholesterol content, and the lowest metabolism was followed by the highest cholesterol content. This was also true for D. E. (case 5), according to the results obtained in November and June (see tables 2 and 3). However, when the result obtained in January is included, the value for concentration of cholesterol seems high for the increased basal metabolism.

ENERGY EXCHANGE

The energy exchange for all five patients is summarized in table 4. The experimental procedure has already been described in this paper and in a previous communication.[1] All determinations were made in duplicate or triplicate.

Since the body weight of these patients fluctuated with the amount of edematous fluid as well as with the muscular development, it was deemed wise to make comparisons on the basis of stature as well as of body weight. We have been unable to find data of a similar nature on

11. Liu, S. H., and Chu, H. I.: An Optimal Diet in Promoting Nitrogen Gain in Nephrosis, J. Clin. Investigation **14**:293 (May) 1935.

TABLE 4.—*Energy Exchange in Nephrosis, per Twenty-Four Hours, Average for Six Day Period*

Patient	Date	Weight, Kg.	Height, Cm.	Intake			Output						Absorption, Percentage	Expenditure in			Ratio of Intake to Basal Metabolism
							Urine			Feces							
				Total Calories	Calories per Kg.	Calories per Cm.	Total Calories	Calories per Kg.	Calories per Cm.	Total Calories	Calories per Kg.	Calories per Cm.		Excreta, Percentage	Basal Metabolism, Percentage	Growth, Digestion, Activity, Percentage	
Case 1, T. D....	10/25-30/32	14.08	92.5	1,385	98.3	15.0	...	...	....	122	8.7	1.32	91.2				
	12/ 7-12/32	16.62	92.5	1,420	85.4	15.4	...	...	....	120	7.2	1.30	91.5				
	2/16-21/32	15.29	92.5	1,463	95.6	15.8	76	4.9	0.82	103	6.7	1.11	93.0	12.2	55.3	32.5	1.6
Average.....	.....	15.33	92.5	1,423	93.1	15.4	76	4.9	0.82	115	7.5	1.24	91.9	12.2	55.3	32.5	1.6
Case 2, L. B....	6/17-22/34	12.89	85.5	1,211	93.9	14.2	63	4.9	0.74	79	6.1	0.92	93.5	11.7	57.1	31.2	1.8
	7/ 5-10/34	13.78	86.1	1,122	81.4	13.0	58	4.2	0.67	84	6.1	0.98	92.5	12.7	68.3	19.0	1.5
Average.....	.....	13.34	85.8	1,167	87.7	13.6	61	4.6	0.71	82	6.1	0.95	93.0	12.2	62.7	25.1	1.7
Case 3, J. M....	10/20-31/33	20.12	106.4	1,888	93.8	17.7	101	5.0	0.95	122	6.0	1.15	93.5	11.8	44.3	43.9	2.3
	12/17-22/33	20.06	107.0	1,058	52.7	9.9	69	3.4	0.64	93	4.6	0.87	91.2	15.3	75.8	8.9	1.3
	2/15-20/34	18.92	107.3	1,550	81.9	14.4	88	4.6	0.82	101	5.3	0.94	93.5	12.2	55.5	32.3	1.8
	4/29-5/7/34	18.96	107.3	1,468	77.4	13.7	91	4.8	0.85	73	3.8	0.68	95.0	11.2	60.4	28.4	1.7
	5/22-27/34	19.54	107.4	1,453	74.3	13.5	102	5.2	0.95	103	5.2	0.96	92.9	14.1	61.0	24.9	1.6
Average.....	.....	19.52	107.0	1,483	76.0	13.8	90	4.6	0.84	98	5.0	0.92	93.4	12.9	59.4	27.7	1.7
Av. 2 normal...	5 yrs.	14.9	99.0	1,471	99.1	14.9	55	3.7	0.56	88	5.9	0.89	94.3	9.7	56.3	34.0	1.8
Case 4, E. L....	7/14-19/31	30.75	137.1	1,408	45.8	10.3	155	5.0	1.13	99	3.2	0.72	93.0	18.0			
	7/25-30/31	29.93	137.1	1,813	60.5	13.2	165	5.5	1.20	219	7.3	1.60	88.0	21.2			
Average.....	.....	30.34	137.1	1,611	53.2	11.8	160	5.3	1.17	159	5.3	1.16	90.5	19.6			
Av. 2 normal...	11 yrs.	27.1	.....	1,927	71.1	....	67	2.5	....	107	4.0	....	94.4	9.0	57.7	33.3	1.7
Case 5, D. E....	10/12-17/32	41.26	164.6	2,472	59.9	15.0	...	...	....	212	5.1	1.29	91.4	....	61.1	....	1.6
	11/15-20/32	44.18	164.6	2,883	65.2	17.5	...	...	....	135	3.0	0.82	95.3	....	42.6	....	2.3
	1/16-21/33	50.25	164.6	2,918	58.0	17.7	...	...	....	126	2.5	0.77	95.7	....	46.9	....	2.1
	2/15-21/33	53.95	164.6	2,803	51.9	17.0	197	3.6	1.20	127	2.3	0.77	95.5	11.6	48.6	39.8	2.1
	5/21-26/33	54.74	164.6	2,464	45.0	15.0	191	3.5	1.16	115	2.1	0.70	95.3	12.4	56.9	30.7	1.8
Average.....	.....	48.88	164.6	2,708	56.0	16.4	194	3.6	1.18	143	3.0	0.87	94.6	12.0	51.2	35.3	2.0
Av. 4 normal...	15 yrs.	46.98	160.0	2,316	50.6	14.5	127	2.7	0.89	103	2.2	0.64	95.5	10.2	59.1	30.9	1.8

nephrotic patients in the literature, and therefore the values for J. M. (case 3), E. L. (case 4) and D. E. (case 5) were compared with the averages for apparently normal children of their respective ages studied previously by us.[12]

In general, the total caloric intake of the five patients increased with their size, but the values in cases 3, 4 and 5 fluctuated widely. J. M. (case 3) showed the most marked variations. The reason for these fluctuations can be explained. In the first period the child was on a regular diet of 1,880 calories. In the second period, the type of food in the modified Schiff diet did not appeal to the taste of the patient, and, partly for this reason, his energy intake was 80 per cent less than in the first period. This same difference is also evident when calculations are made on the basis of weight and height, since neither of these changed appreciably. In subsequent periods his total caloric intake never was as great as in the first period and was low for his size. However, the average total caloric intake for the five periods was almost identical with the average for two normal children of his age, but his caloric intakes per kilogram and per centimeter were markedly below the normal values.

The caloric intake of E. L. (case 4) was lower with the low protein diet (1,408 calories) than with the high protein diet (1,813 calories). In the latter period the values obtained for her compared favorably with those for two normal girls of her age. The question may well be raised whether it is advantageous to keep such patients on a high caloric level. For example, for D. E. (case 5) the caloric intake averaged 2,708 calories, which was higher than the average for four normal girls of her age. On the basis of body weight or height the energy values were also correspondingly higher than normal. This patient was greatly undernourished, and it was thought advisable to give her a diet of higher energy value than she would voluntarily have selected. With this diet she maintained a satisfactory clinical condition.

The total loss of energy through the kidneys appeared to vary with the size of the patient, the intake of protein and the urinary albumin. The data in table 4 show that there was a direct relationship between the size of the patient and the urinary loss of energy. This was also true when values were expressed in calories per centimeter. However, when these values were calculated on the basis of body weight the loss of energy for all patients except D. E. (case 5) was of the same order of magnitude.

12. Wang, C. C.; Kern, R.; Frank, M., and Hayes, B. B.: Metabolism of Undernourished Children: II. Basal Metabolism, Am. J. Dis. Child. **32**:350 (Sept.) 1926. Wang, C. C.; Frank, M., and Kaucher, M.: Metabolism of Undernourished Children: VI. Caloric Balance, ibid. **36**:979 (Nov.) 1928. Wang, Kaucher and Wing.[1]

When the average urinary losses of energy of J. M. (case 3), E. L. (case 4) and D. E. (case 5) were compared with those of apparently normal children of their respective ages, it was shown that the nephrotic patients lost much more energy in the urine, irrespective of the method of comparison. The magnitude of this difference appeared to depend on the amount of albumin in the urine. For example, E. L. (case 4) and D. E. (case 5), who excreted large amounts of albumin in the urine, showed a much higher loss of energy than normal. In E. L. (case 4) the influence of intake of protein could not be ascertained because of the high excretion of albumin. This might have been true also in D. E. (case 5) if the urinary loss of energy had been determined in periods when the intake of proteins varied. The influence of the intake of protein on urinary loss of energy was clearly shown in J. M. (case 3), whose excretion of albumin was low. In this patient there was an increased loss of energy with each increase in the intake of protein.

The fecal loss of energy varied inconsistently in its relation to the size or the age of the child and to the intake of calories, protein or fat. In general, the values for the nephrotic patients were definitely higher than the corresponding values for normal children of their respective age groups.

The percentage absorption of energy of the five patients is given in table 4, and the average values of the older children are compared with values obtained by us for normal children of their ages. Except for the first period of D. E. (case 5), when she was losing weight rapidly (chart 2), the values were identical with those of the four normal children. The values found for the four younger children appear to indicate that the percentage of absorption was slightly lower than that of our normal group.

The expenditure of energy, which includes loss in excreta, basal metabolism, growth, digestion and activity, has been calculated and is expressed in percentages in table 4. Although the number of determinations and the number of values for normal persons in our group were small, it is suggested from the variations obtained that the nephrotic child in this respect is not different from the normal child. In spite of the variations in physical condition of the nephrotic children and of the frequent changes in their diets, the average ratio of caloric intake to basal metabolism remained close to the value found for normal children.

SUMMARY

Metabolic studies on five nephrotic children, two boys and three girls between the ages of 3 and 16 years, were made during periods lasting from forty-two to two hundred and fifty-five days. In this report the clinical data, the effect of various treatments and the records of

excretion of urinary protein, studies of the blood, basal metabolism and the energy exchange are presented.

The effects of diuretics and dietary treatment varied greatly in producing temporary changes. However, no prolonged general improvement, including disappearance of edema, was accomplished with any procedure.

The protein content (albumin and globulin) of the serum, its nonprotein nitrogen content and the cholesterol content of the blood were determined from time to time for the five patients. The values were those characteristic for the nephrotic syndrome; i. e., there were a low total protein content, a reversal of the ratio of albumin to globulin, a normal value for serum nonprotein nitrogen, except in two patients in whom the nephrotic syndrome was complicated, and a high content of blood cholesterol. The concentration of hemoglobin and the cell counts showed no definite changes.

The basal metabolism and the energy exchange are discussed in relation to age, height and weight. The values are compared with data reported for normal children. The values for basal metabolism of all patients were within normal limits according to the standard of Benedict and Talbot and, with one exception, to the standard of Harris and Benedict. According to Dreyer's standard the heat production of all patients except one (case 5) was low. From the determinations of caloric intake and caloric loss, calculations were made for the percentage absorption of energy and the expenditure of energy for growth, digestion and activity. These values agreed with data obtained for normal children. This indicates that the energy exchange of a nephrotic patient is normal.

MEASUREMENT OF OBESITY BY THE CREATININE COEFFICIENT

NATHAN B. TALBOT, M.D.

WITH THE ASSISTANCE OF FRANCES BROUGHTON

BOSTON

Obesity is usually defined as an excessive accumulation of fat in the body. On this basis the diagnosis of obesity in overweight children is not difficult and is usually made by cursory examination. Obesity is more strictly defined, however, as an accumulation in the body of an amount of subcutaneous fat which is excessive in relation to the amount of muscle. Persons of normal weight who show such a disproportion should be considered obese. It follows as a corollary that the person who is overweight but has superior development of the muscular system should not be considered obese. The present study was undertaken to show that by means of clinical examination and determination of the creatinine coefficient obesity as just defined may be quantified.

Clinicians note marked contrast in the relative thicknesses of superficial fat and of underlying muscle in lean and corpulent children. By means of inspection and palpation a trained observer may distinguish lean, average and obese children, but differences in technic and in the interpretation of observations make it difficult to compare the conclusions of one observer with those of another. This difficulty of comparison leads to a search for some method by which the degree of obesity may be quantified. So far as can be found, there is no accurate method available for estimating the ratio of muscle to body weight. The approximation method, which takes into account the deviation in body weight from the normal average of weight for height, was at one time considered a reliable index of obesity but is not now generally accepted because of differences in types of body build. A further possibility lies in the estimation of the rate of excretion of creatinine.

CREATININE COEFFICIENT

In the exhaustive monograph of Hunter,[1] the thesis that the excretion of creatinine is a product of muscular catabolism and hence an index of muscle mass is discussed at length. This conception has grown

From the Department of Pediatrics, Harvard University Medical School, and the Infants' and Children's Hospitals.

1. Hunter, A.: Creatine and Creatinine, Monograph on Biochemistry, New York, Longmans, Green & Co., Ltd., 1928.

out of the work done by Folin in 1904 [2] and has since been repeatedly confirmed.[3] The excretion of creatinine is surprisingly uniform from day to day provided the collection of urine is accurate. Palmer, Means and Gamble [4] expressed the belief that constancy justifies making only one or two determinations of the twenty-four hour output of creatinine. Differences between persons are dependent largely on variations in the muscle mass. The proportion of muscle in the body may be derived from the ratio of the amount of creatinine excreted in the urine to body weight. This ratio, $\frac{\text{milligrams of creatinine per twenty-four hours}}{\text{kilograms of body weight}}$, was named the creatinine coefficient by Shaffer.[5] To "differences in the creatinine coefficient may be ascribed differences in the relative amount of metabolically inert substance associated with the active tissues, and especially to differences in adiposity" (Hunter [1]). Under most circumstances, a low creatinine coefficient is an index of obesity.

Shaffer [5] found that the creatinine coefficients of normal men vary from 14.5 to 31.4. He expressed the belief that coefficients below 18.8 are to be found only in elderly and excessively fat or inactive and poorly developed subjects. Shaffer, and also Hodgson and Lewis [6] and Tracy and Clark,[7] pointed out that women, who are known to have more adipose and less muscular tissue than men, have correspondingly lower coefficients. Women of well developed musculature, on the other hand, have coefficients comparable to those of men.[6] McLaughlin and Blunt [8] found the excretion of creatinine of underweight women to be greater than that of normal women. From this they concluded that underweight may indicate only an absence of the usual deposits of fat in the body. Recently, McClugage, Booth and Evans [9] reported on the excretion of creatinine of 5 obese and 5 underweight adults. They found that without exception patients with well developed muscles have high creatinine coefficients, while those with low creatinine coefficients either have poorly developed muscles or are excessively obese. By fol-

2. Folin, O.: Beitrag zur Chemie des Kreatinins und Kreatins im Harne, Ztschr. f. physiol. Chem. **41**:223, 1904; cited by Hunter.[1]

3. See Hunter [1] for further references.

4. Palmer, W. W.; Means, J. H., and Gamble, J. L.: Basal Metabolism and Creatinine Elimination, J. Biol. Chem. **19**:239, 1914.

5. Shaffer, P. A.: The Excretion of Kreatinin and Kreatin in Health and Disease, Am. J. Physiol. **23**:1, 1908.

6. Hodgson, P., and Lewis, H. B.: Physical Development and the Excretion of Creatine and Creatinine by Women, Am. J. Physiol. **87**:288, 1928.

7. Tracy, M., and Clark, E. E.: The Excretion of Creatinine by Normal Women, J. Biol. Chem. **19**:115, 1914.

8. McLaughlin, L., and Blunt, K.: Some Observations on the Creatinine Excretion of Women, J. Biol. Chem. **58**:285, 1923.

9. McClugage, H. B.; Booth, G., and Evans, F. A.: Creatin Excretion in Abnormal States of Nutrition, Am. J. M. Sc. **181**:349, 1931.

lowing the excretion of creatinine during a prolonged period of reduction in weight, they were able to show that the excess weight in the obese is due to adipose tissue.

Working with children, Denis and Kramer [10] showed that in undernourished children the excretion of creatinine per kilogram is slightly higher than that in children of normal weight. Utheim,[11] on the other hand, found the coefficient to be somewhat lowered in infants in a poor nutritional state. Wang and her co-workers [12] were the first to explain this discrepancy by demonstrating a tendency for the creatinine coefficient to rise until the children become approximately 10 per cent underweight and then to show a slight drop. Wang, Genther and Hogden [13] and Rougichitch [14] concluded that there is a close relationship between the excretion of creatinine and the active protoplasmic mass and that changes in the creatinine coefficients reflect changes in the proportion of this mass to body weight.

The measurements in the investigations cited were aimed largely at establishing the general principles of a relation between the creatinine coefficient and changes in weight in relation to height. In none of these, however, has there been a systematic correlation between the degree of adiposity and the creatinine coefficient.

Age is known to be related to the output of creatinine. In infants and children the coefficient is lower than it is in adults. According to Hunter,[1] it is around 2.7 at birth. It rises to from 5.5 to 8 within the first few months; in the third year it is from 11 to 13, in the ninth, between 13 and 19. Recently Wang, Genther and Hodgen [13] found the coefficient in 23 adolescent girls to run from 19.5 to 26.4, with an average of 22.8. They expressed the belief that the coefficient may be as high in adolescence as in adult life, or even higher. Although there is a rise in the coefficient from birth to puberty, the periods of greatest rise are found during the first four years and during the adolescent period, from the twelfth to the sixteenth year. This finding conforms closely to Scammon's graph,[15] which shows the postnatal growth of the

10. Denis, W., and Kramer, J. G.: Influence of Protein Intake on Creatine Excretion in Children, J. Biol. Chem. **30**:189, 1917.

11. Utheim, K.: Metabolism Studies in Infants Suffering from Chronic Nutritional Disturbances, Am. J. Dis. Child. **22**:329 (Oct.) 1921.

12. Wang, C. C.; Frank, M.; Kern, R., and Hays, B. B.: Metabolism of Undernourished Children: III. Urinary Nitrogen with Special Reference to Creatinine, Am. J. Dis. Child. **32**:360 (Sept.) 1926.

13. Wang, C. C.; Genther, I., and Hogden, C.: Metabolism of Adolescent Girls: III. Excretion of Creatinine and Creatine, Am. J. Dis. Child. **51**:1268 (June) 1936.

14. Rougichitch, O. S.: Uric Acid and Creatinin in the Urine of Infants, Am. J. Dis. Child. **31**:504 (April) 1926.

15. Harris, J. A.; Jackson, C. M.; Paterson, D. G., and Scammon, R. E.: Measurement of Man, Minneapolis, University of Minnesota Press, 1930, p. 192.

musculature as a whole in terms of postnatal increments. The periods of rapid growth in musculature are from birth to the sixth year and from the twelfth to the sixteenth year. Correspondingly, in the period from the fifth or sixth to the eleventh or twelfth year there is relatively little change in the creatinine coefficient or in the average normal muscle mass per kilogram.

The measurements in the present investigation were undertaken to establish more exactly the relationship between the coefficient and the clinical presence or absence of obesity. The measurements were confined largely to the middle period of childhood. During this period there is great variation in size and shape, which should serve to emphasize any correlations found.

PLAN OF EXPERIMENT

A group of 37 children were chosen from the wards and the outpatient department of the Children's Hospital. An estimate was made of the proportion of subcutaneous fat to underlying muscle by inspection and by palpation of the abdominal wall and the extremities, with the muscles partially contracted. Those who appeared to have an accumulation of fat that was unusually large in proportion to underlying muscle (12 subjects) were placed in group I; the children who were placed in group II (15 subjects) appeared normal, and those who appeared to have little subcutaneous fat and unusually well developed muscles (6 subjects) formed group III. Children who showed extreme wasting of subcutaneous tissues and muscle and whose bones were unusually prominent (4 subjects) were in group IV. Three of the last group were convalescing from poliomyelitis.

The twenty-four hour specimen of urine was collected with great care. Special instructions [16] were given to each parent and child, outlining the exact steps for the collection. When the specimen was delivered to us, questions were asked to determine whether the collection was accurately timed and complete. Incomplete collections were discarded. The creatinine was determined by Folin's method.[17] The children were weighed in their nightclothes or underwear, except in a few instances in which no clothes were worn. (See table.)

16. Directions for Collection of Urine:

1. Start collection on the morning of the day before the appointment. If the patient is at school, collect on the Saturday or Sunday before the appointment.

2. Obtain for the collection a clean 2 quart (1,893 cc.) bottle with a stopper. Put 5 cc. of toluene (obtained from the hospital pharmacy) in the bottle and keep on ice or in the coolest place possible.

3. Have the patient void at exactly 7 a. m. on the morning on which you start the collection. Do not let him void between 6 and 7 a. m., as if he does so he may not be able to void at the specified time. Discard that specimen.

4. Thereafter collect all the urine voided during the next twenty-four hours, that is, until 7 a. m. of the following day. Again, do not let patient void between 6 and 7 a. m., but have him void at exactly 7 a. m. Save that specimen.

5. During the collection period have the patient void urine before moving his bowels, so that no urine will be lost with the stool.

6. Let us know if for any reason these directions have not been followed exactly.

17. Folin, O.: Laboratory Manual of Biological Chemistry, ed. 5, New York, D. Appleton-Century Company, Inc., 1934, p. 159.

Observations on the Creatinine Coefficient in Relation to the Clinical Presence or Absence of Obesity

Case	Age, Years	Weight, Kg.	Height, Cm.	Variation in Weight from Normal for Height and Age,* Percentage	Creatinine for Twenty-Four Hours, Mg.	Creatinine Coefficient	Estimated Percentage of Muscle Weight to Body Weight
			Group I (Obese Children)				
R. L.	11	54.0	165.8	+ 4	667	12.3	
R. M.	12	48.5	153.1	+14	638	13.1	
M. D.	10	42.7	142.2	+22	745	17.4	
J. C.	5 3/12	32.4	128.3	+25	400	12.3	
E. N.	9	41.1	137.0	+30	708	17.2	
D. F.	9	47.2	142.2	+37	537	11.4	
C. S.	7	45.4	139.7	+39	752	16.5	
E. B.	11 4/12	50.7	143.5	+41	609	12.0	
H. S.	10	59.2	152.4	+43	885	15.0	
F. R.	9 10/12	60.3	152.4	+46	952	15.8	
M. R.	9	47.0	137.0	+49	640	13.6	
A. G.	12 7/12	95.6	173.5	+61	1,108	11.6	
Average						14.0	25
Range				+4 to +61		11.4 to 17.4	
			Group II (Normal Children)				
F. G.	8	18.2	125.1	−27	387	21.3	
G. F.	8 5/12	22.0	129.5	−20	423	19.2	
M. Q.	12	25.2	132.1	−17	667	26.4	
E. G.	5 3/12	14.0	96.0	−10	385	27.5	
D. M.	8 10/12	23.4	122.0	− 2	467	20.0	
G. L.	9	30.3	128.3	− 2	618	20.4	
G. B.	9	30.5	139.0	0	620	20.3	
B. F.	10 4/12	31.6	137.2	0	520	16.5	
G. Z.	11 2/12	30.0	133.4	0	460	15.3	
C. B.	7 5/12	22.5	118.7	0	456	20.3	
G. B.	11	30.8	129.5	+ 4	731	23.7	
B. L.	10	38.9	144.8	+ 5	640	16.4	
E. F.	9	32.9	136.6	+ 6	693	21.0	
F. K.	7 9/12	20.8	106.5	+12	395	19.0	
R. S.	10 4/12	29.1	125.7	+14	578	19.8	
Average						20.5	37
Range				−27 to +14		15.3 to 27.5	
			Group III (Lean Children)				
L. H.	7 9/12	15.0	115.5	−29	557	37.1	
W. M.	8 5/12	19.9	123.2	−19	557	28.0	
R. S.	7 8/12	16.3	109.0	− 7	655	40.2	
R. H.	8 2/12	27.4	131.5	− 3	910	33.2	
K. S.	13 11/12	60.5	167.6	+ 9	1,456	24.1	
F. B.	10 5/12	25.6	132.1	+12	545	21.3	
Average						30.7	55
Range				−29 to +12		21.3 to 40.2	
			Group IV (Emaciated Children)				
C. M.	9 4/12	22.5	134.6	−26	244	10.8	
F. C.	6 10/12	21.8	130.0	−19	235	10.8	
E. B.	13	30.2	.....	....	153	5.0	
R. D.	11 6/12	21.9	.....	....	205	9.4	
Average						9.0	16
Range						5.0 to 10.8	

* Baldwin-Wood tables.

COMMENT

The experiments of Chanutin [18] and Benedict and Osterberg [19] "definitely establish the origin of urinary creatinine from creatine," (Hunter [1]). The excretion of creatinine parallels the amount of creatine in the body or (for practical purposes) in the muscles, because 98 per cent of the total creatine in the body is in the muscles. If this is admitted, "it follows as an obvious corollary that, so long as the muscles possess a constant creatine content, urinary creatinine is proportional to muscle mass." [1] As early as 1913 Myers and Fine [20] and in 1919 Burger [21] deduced from this that the weight of muscles can be calculated from the output of creatinine. Burger calculated that 1 Gm. of urinary creatinine per day corresponds to 22.9 Kg. of muscle. This value involves an arithmetical error and will therefore not be used.

If the body weight, the excretion of creatinine and the muscle weight are known, the number of kilograms of muscle per gram of creatinine is easily found. According to Vierordt,[22] the muscles of the new-born infant make up 25.1 per cent of the total body weight and those of a "normal" adult man, 43 per cent. According to Hunter, the average creatinine coefficient of infants is 10.1. Marples and Levine [23] recently reported that the coefficient does not vary between the third week and the seventh month of life. The average coefficient of infants studied by them was 14.0. Because this figure represents the result of careful measurements, it will be considered the approximate "normal" coefficient for infants. The average coefficient for adult males approximates 24.0.[24] A normal infant weighing 5 Kg. may be assumed, then, to possess 1.25 Kg. of muscle. His output of creatinine is 70 mg. per twenty-four hours. One gram of urinary creatinine per day corresponds, for the infant, to 17.8 Kg., and for the man, to 17.9 Kg., of muscle. Contrary to reports in the literature, it would appear, therefore, that

18. Chanutin, A.: The Fate of Creatine When Administered to Man, J. Biol. Chem. **67**:29, 1926.

19. Benedict, S. R., and Osterberg, E.: Studies in Creatine and Creatinine Metabolism: V. The Metabolism of Creatine, J. Biol. Chem. **56**:229, 1923.

20. Myers, V. C., and Fine, M. S.: The Creatine Content of Muscle Under Normal Conditions: Its Relation to the Urinary Creatinine, J. Biol. Chem. **14**:9, 1913.

21. Burger, M.: Beiträge zum Kreatininstoffwechsel, Ztschr. f. d. ges. exper. Med. **9**:262, 1919; cited by Hunter.[1]

22. Vierordt, H.: Daten und Tabellen für Mediziner, ed. 3, Jena, Gustav Fischer, 1906.

23. Marples, E., and Levine, S. Z.: Creatinuria of Infancy and Childhood: I. Normal Variations; Creatine Tolerance Tests and the Effect of Amino-Acetic Acid in Normal Infants, Am. J. Dis. Child. **51**:30 (Jan.) 1936.

24. Hunter [1] gave this average in table 13, p. 124. The range is from 21.8 to 25.0.

the excretion of creatinine of infants is directly comparable to that of adults.

The accuracy with which the creatinine coefficient reflects changes in the ratio of active protoplasm to fat depends on the constancy with which bone and water are present in persons of the same weight. In this discussion no attempt will be made to distinguish between fat and water, although there may be considerable variation. No cases of dehydration or edema are included. At the present time there is no satisfactory method of measuring bone weight in living persons. For this reason, bone is disregarded as a variable in these studies, except in cases in which the proportion of bone to muscle and subcutaneous tissue is strikingly increased.

The average creatinine coefficients of obese, normal, lean and emaciated children are 14.0, 20.5, 30.7 and 9.0, respectively (table 1). The estimated muscle weight of these groups constitutes 25, 37, 55 and 16 per cent, respectively, of the total body weight. These figures show a close correlation between the creatinine coefficient and the apparent proportion of muscle to body weight. In the normal group the coefficients approximate those of the obese on one hand and those of the lean children on the other. This is not surprising, in view of the simplicity of the clinical methods used in the grouping. The emaciated children in group IV had the lowest creatinine coefficients of the entire group. They showed that a low creatinine coefficient is not always associated with obesity. The clinical difference between emaciation and obesity is so distinct, however, that little difficulty should be encountered in distinguishing between them. Therefore, when a diagnosis of the degree of obesity derived from an accurately determined creatinine coefficient is at variance with clinical findings, a diagnosis of some disease involving the musculature should be considered.

The estimated percentage of body weight consumed in muscles in group I was 25, as compared with an average of 55 per cent in group III. The difference between these percentages demonstrates the profound variation in composition between the bodies of fat and of lean persons. The active protoplasmic mass per kilogram of body weight of the average lean child is approximately twice that of the obese child. That there should be such a range in composition is not surprising, in view of the marked differences in size, shape and composition of the bodies observed clinically and at necropsy. The child whose body was of average composition, represented in the normal group, had a musculature lying approximately half-way between those of the extreme groups. The data at hand suggest that during the middle period of childhood the muscles constitute 37 per cent of the weight of the normally developed child. This agrees closely with the figure of 37.5 per cent calculated from Scammon's graph for 9 year old children.

In table 1 the grouping was based on differences in the clinical appearance of the children studied. When the same children were regrouped according to the generally accepted standards of normal weight for height and age, those who were more than 20 per cent overweight showed an average creatinine coefficient of 14.5; those between plus 20 per cent and minus 10 per cent, a coefficient of 21.0, and those more than 10 per cent below normal, a coefficient of 21.9. All the overweight children were clinically obese and had creatinine coefficients between 11.0 and 17.4. Of the 18 children whose weights were within normal limits, 12 were clinically normal and had coefficients ranging between 15.3 and 27.5; 4 appeared to be lean, and 2 showed an excessive accumulation of fat in proportion to their muscles. Their creatinine coefficients were 12.3 and 13.1, respectively. These children were just as obese as any of the overweight children. It is clear that obesity may be gaged more accurately by clinical inspection and the creatinine coefficient than by the height-weight standards.

The data presented are too few to warrant an analysis of the standard deviation. Such treatment would require a much greater number of cases than we have treated in this preliminary report. The groups showed considerable spread, but with greater numbers more groups could have been demarcated (certainly a moderately obese group should include children who at present are on the borderline between normal and obese). The percentage of variation in the creatinine coefficients within each group depends on the clinical evaluation, which is assumed to be correct, and in the comparison of these two standards all the error in this method of calculation is thrown on the creatinine coefficient. Further data may show the greater part of the error to be in the clinical appraisal.

The inconvenience associated with the determination of the creatinine coefficient precludes its general use as an index of obesity. The standards of normal weight for height and age may serve as a rough guide for the clinician in his estimate of configuration and composition of the bodies of children. Those who use the standards of height and weight, however, should appreciate that they are not accurately informative as to the proportion of muscle to adipose tissue. An accurate quantitative estimate of this proportion, and hence of the degree of obesity, may be derived from the creatinine coefficient.

SUMMARY AND CONCLUSIONS

The evidence for considering creatinine as an index of muscle mass is reviewed.

An inquiry is made into the quantitative estimation of obesity by means of the creatinine coefficient, and the following conclusions are drawn:

1. Obesity, strictly defined as an accumulation of subcutaneous fat which is excessive in relation to the amount of muscle, is found not only in children who are overweight for their height but also in children of normal weight for their height. Changes in weight for height are neither qualitatively nor quantitatively accurate as an index of obesity.

2. The average creatinine coefficients of obese, normal and lean children were found to be 14.0, 20.4 and 30.7 respectively. The weight of the muscles, as calculated from the output of creatinine of these groups, constitutes, respectively, 25, 37 and 55 per cent of the body weight. A small group of children with marked emaciation had an average creatinine coefficient of 9.0, and their muscles were calculated to yield 16 per cent of the body weight.

3. The creatinine coefficient, combined with clinical appraisal, is an accurate index of obesity. Physiologic and pathologic problems concerned with the relative amount of muscle in the body may be studied by the determination of the excretion of creatinine.

Dr. Alfred T. Shohl made suggestions for the preparation of this paper.

RESULTS OF SCHICK TEST IN 5,195 CHILDREN GIVEN INJECTIONS OF DIPHTHERIA TOXOID

BEN. BENJAMIN, M.D.
AND
GRANT FLEMING, M.D.
MONTREAL, CANADA
AND
MARY A. ROSS, PH.D.
TORONTO, CANADA

The Child Welfare Association of Montreal began active immunization against diphtheria of children attending its health centers throughout the city in May 1926, and this work has been carried on as an integral part of its health program since then. This study covers the period from May 1926 until the end of 1934.

At first, groups of children over 1 year old were inoculated at a number of health centers just as soon as a convenient number of cards were signed by parents signifying their desire to have their children treated, after the nurses had explained the advisability and urgency of having this done. As a result of the launching of this campaign against diphtheria, over 1,200 children were given injections during the first year. During the following year, immunization against diphtheria was introduced in every health center, and diphtheria toxoid was administered to each child when he or she had reached the age of 1 year unless the parents refused to have it done, which occurred rarely. Later, the age at which immunization was advised was reduced to six months.

ADMINISTRATION OF DIPHTHERIA TOXOID

After Ramon had demonstrated excellent active immunization in guinea-pigs and horses by means of injections of diphtheria toxoid (anatoxin), his collaborators proceeded to administer this antigen to human beings, especially children, with similarly good results. The percentage of immune persons after the use of diphtheria toxoid was shown to be considerably greater than that which had been obtained theretofore after injections of a mixture of toxin and antitoxin. Toxoid had the additional advantages that it contained no free toxin and no ani-

From the Child Welfare Association of Montreal, the Department of Public Health and Preventive Medicine, McGill University, and the Department of Epidemiology and Biometrics, School of Hygiene, University of Toronto.

mal serum. It was therefore decided to use this product in the health centers of the Child Welfare Association.

Diphtheria toxoid (anatoxin-Ramon) prepared by the Connaught Laboratories of the University of Toronto and properly tested as to potency was injected subcutaneously in the deltoid region of the arm in all cases. At first, two doses of 0.5 and 1 cc., respectively, were given at an interval of three weeks or one month, as recommended by Ramon and his associates [1] and by Fitzgerald; [2] then some children were given two doses of 1 cc. each. Later, as it had been found by Ramon [3] and others [4] that a considerably greater number of persons given three doses gave a negative Schick reaction from two to three months after inoculation than did the subjects who received two doses, all children were given three doses, in some centers at intervals of three weeks and in others at intervals of one month. In a large group the three doses of diphtheria toxoid injected consisted of 0.5, 0.5 and 1 cc., respectively, i. e., a total of 2 cc., and in a larger group they consisted of 0.5, 1 and 1 cc., respectively, i. e., a total of 2.5 cc.

It might be of interest to mention that less than 1 per cent of the children showed anything more than the small local area of erythema which not infrequently occurs in the first twenty-four hours after the injection of diphtheria toxoid and fades usually within forty-eight hours and that severe local reactions or general reactions with fever were extremely rare. This is in keeping with previous observations recorded by Ramon,[5] Fitzgerald [2] and others. In this regard, it is important to appreciate that the children studied belonged to the younger age groups; 88 per cent were 5 years or under. A small number of children who received a first injection of diphtheria toxoid were not brought back for subsequent doses to complete their immunization owing to unavoidable circumstances.

---

1. Roubinovitch, J.; Loiseau, G., and Laffaille, A.: Immunisation antidiphtérique chez l'enfant avec l'anatoxine diphtérique, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:782, 1924. Darré, H.; Loiseau, G., and Laffaille, A.: De l'immunisation antidiphtérique par l'anatoxine diphtérique, ibid. **48**:729, 1924. Martin, L.: Sur l'immunisation antidiphtérique avec l'anatoxine, Bull. Acad. de méd., Paris **91**:523, 1924.

2. Fitzgerald, J. G.: Diphtheria Toxoid as an Immunizing Agent, Canad. M. A. J. **17**:524, 1927.

3. Ramon, G.: L'anatoxine diphtérique dans son application à l'immunisation active de l'homme et à la prophylaxie de la diphthérie, Ann. Inst. Pasteur **45**:291, 1930.

4. Park, W. H.: Weekly Bull., New York Dept. Health, Feb. 6, 1932, no. 5.

5. Ramon, G.: La prophylaxie de la diphtérie et la vaccination par l'anatoxine diphtérique, Rev. d'hyg. **49**:401, 1927.

SCHICK TESTS

Because of the high susceptibility of young children to diphtheria, as shown by von Gröer and Kassowitz [6] and by Park and Zingher,[7] and since healthy young children may give a negative Schick reaction and yet have little circulating antitoxin, as reported by Jensen,[8] no Schick tests were done previous to immunization. Six months after the last injection of diphtheria toxoid parents were requested to bring the children for Schick testing, the first Schick tests being performed in July 1927. All the Schick tests were administered by the late Dr. A. B. Chandler and by one of us (B. B.). Most of the tests were performed on the anterior surface of the forearm by the intradermal injection of 0.1 cc. of a dilution of diphtheria toxin containing a fiftieth of the minimum lethal dose, and a considerable number were similarly performed on the posterior part of the arm. The material used for the Schick tests was properly tested as to potency, was prepared by the Connaught Laboratories of the University of Toronto and conformed to the requirements recommended by the League of Nations.[9] No control injection was done in the vast majority of the Schick tests, as the number of pseudoreactions in very young children has been found to be of little significance.[7b] This was confirmed in about 200 Schick tests which were performed with accompanying control injections of 0.1 cc. of 1:100 toxoid, as no definite sensitivity to diphtheria protein was observed. The reactions to the Schick tests were read after two days up to 1930, and thereafter four days and occasionally five or six days after the tests were done. A certain number of children who showed no reaction were seen only by a nurse, while all positive or doubtful reactions were passed on by the physicians who performed the tests.

It was reported by Ramon [8] that children who gave a positive Schick reaction after three doses of toxoid became immune after a fourth dose. Therefore, children who showed at first a positive or a doubtful reaction were given another subcutaneous injection of 1 cc. of diph-

6. von Gröer, F., and Kassowitz, K.: Studien über die normale Diphtherieimmunität des Menschen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **23**:108, 1914.

7. (*a*) Park, W. H., and Zingher, A.: Diphtheria Immunity: Natural Active and Passive; Its Determination by the Schick Test, Am. J. Pub. Health **6**:431, 1916. (*b*) Zingher, A.: Active Immunization of Infants Against Diphtheria, Am. J. Dis. Child. **16**:83 (Aug.) 1918.

8. Jensen, C.: Sur l'importance de la réaction de Schick négative chez les enfants non immunisés et des enfants immunisés avec l'anatoxine diphtérique, Compt. rend. Soc. de biol. **108**:555 (Nov. 6) 1931.

9. Fraser, D. T., in Report of the Permanent Commission on Biological Standardization (London), Series of League of Nations Publications, no. C. H. 1056 (I), Boston, World Peace Foundation, 1931.

theria toxoid, usually some days afterward, and were again tested four months later up to 1930, and thereafter six months after the fourth dose of toxoid.

For many reasons inherent in a large city population a great number of children who were given complete courses of toxoid were not available later for testing, so that 5,195 of a total of 9,620 were tested.

It is recognized that the Schick test has a limited application in the estimation of immunity to diphtheria. That diphtheria occasionally occurs in a person who reacts negatively to the Schick test is well known. O'Brien, Okell and Parish [10] reported that 18 persons had diphtheria among about 20,000 who had at one time or another reacted negatively. The disease was mild in all of them and in some was apparently "tonsillitis" in a carrier giving a negative Schick reaction. Dudley, May and O'Flynn [11] observed 23 mild attacks among 900 boys 90 per cent of whom gave negative reactions; 19 of the 23 had given negative reactions.

Of all the children immunized by us who gave a negative Schick reaction, 1 girl acquired diphtheria five years after a test eliciting a negative reaction. She had been given three doses of toxoid, of 0.5, 0.5 and 1 cc., respectively, at intervals of three weeks, beginning at the age of 1 year and 8 months, and gave a negative reaction when tested eight months after the last injection of toxoid. Corynebacterium diphtheriae was obtained repeatedly in cultures of material from her throat (tonsils), and a test for virulence produced a positive result. The disease was mild, and she made an uninterrupted recovery. Another child, a boy, was said to have died of diphtheria at the age of 2 years and 7 months. He had been given a first dose of 0.5 cc. when he was 1 year and 8 months old, 0.5 cc. one month later and 1 cc. a month thereafter. His reaction to the Schick test was negative six months after the third injection of toxoid. He died at home after an illness of two days, forty-two days after a negative reaction to the Schick test had been elicited. No laboratory confirmation of the diagnosis was obtained.

There is a wide variation in the antitoxin content of the blood in different persons who react negatively to the test. Schick [12] has often been quoted as having determined that a person requires $\frac{1}{30}$ unit of antitoxin per cubic centimeter of serum in order to give a negative reac-

10. O'Brien, R. A.; Okell, C. C., and Parish, H. J.: "Diphtheria" in Schick-Negative Reactors, Lancet **1**:149 (Jan. 19) 1929.

11. Dudley, S. F.; May, P. M., and O'Flynn, J. A.: Active Immunization Against Diphtheria, Medical Research Council, Special Report Series, no. 195, London, His Majesty's Stationery Office, 1934.

12. Schick, B.: Determining Immunity Against Diphtheria, Weekly Bull., New York Dept. Health, Jan. 5, 1929. Park, W. H., and Dickson, A. J., in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1925, vol. 6, p. 96.

tion. Ramon and Debré,[13] on the basis of studies carried out on a group of 105 school children who had been given injections of toxoid, concluded that it was necessary to have at least this amount of antitoxin to give a negative reaction, and that criticism directed against this conclusion was unwarranted. However, it has been clearly demonstrated in a number of reliable communications that this figure has been greatly overestimated. Schick, von Gröer and Kassowitz[14] stated that a Schick reaction became indefinite when the serum contained $\frac{1}{500}$ (0.002) unit and negative when $\frac{1}{200}$ (0.005) unit per cubic centimeter of serum was reached. Jensen[8] observed some healthy children over 2 years old with less than $\frac{1}{2,000}$ (0.0005) unit per cubic centimeter of serum who gave negative Schick reactions, and concluded that the level at which a negative reaction is obtained presents considerable individual variation above and below $\frac{1}{30}$ unit. Glenny and Waddington[15] came to the conclusion that a concentration of antitoxin in the blood of $\frac{1}{250}$ unit per cubic centimeter of serum corresponds to the level at which a negative Schick reaction is obtained in guinea-pigs. Parish and Wright[16] mentioned the occasional occurrence of diphtheria in a person giving a negative Schick reaction and stated that a person may react negatively and have as little as $\frac{1}{250}$ to $\frac{1}{500}$ unit per cubic centimeter of serum. The results of Fraser and Halpern[17] and of Brandon and Fraser[18] indicate that the level at which a negative Schick reaction is obtained is about $\frac{1}{250}$ unit of antitoxin per cubic centimeter of serum. Dudley, May and O'Flynn[11] placed the level of immunity, for practical purposes, at $\frac{1}{100}$ unit.

Having clearly outlined the inadequacy of the Schick test as an exact measure of immunity to diphtheria, we nevertheless feel justified in stating that its practical value in the determination of susceptibility to the development of clinical diphtheria in most cases is definitely established. Moloney and Fraser[19] summed up the situation by concluding

13. Ramon, G., and Debré, R.: Persistance et valeur de l'immunité antitoxique chez les sujets vaccinés au moyen de l'anatoxine diphtérique, Presse méd. **38**:841 (June 21) 1930.

14. Schick, B.; von Gröer, F., and Kassowitz, K.: Methodik und Technik des Erforschung der normalen antitoxischen Diphtherieimmunität des Menschen, in Abderhalden, E.: Handbuch der biologischen Arbeitsmethoden, Berlin, Urban & Schwarzenberg, 1924, vol. 1, sec. 13, pt. 2, p. 531.

15. Glenny, A. T., and Waddington, H.: The Schick Reaction and Circulating Antitoxin, J. Path. & Bact. **32**:275, 1929.

16. Parish, H. J., and Wright, J.: The Schick Test and Active Immunization in Relation to Epidemic Diphtheria, Lancet **1**:600 (March 16) 1935.

17. Fraser, D. T., and Halpern, K. C.: Diphtheria Toxoid, Canad. Pub. Health J. **26**:469, 1935.

18. Brandon, K. F., and Fraser, D. T.: Observations on the Interpretation of Schick Tests, J. Immunol. **31**:387, 1936.

19. Moloney, P. J., and Fraser, C. J.: Immunization with Diphtheria Toxoid (Anatoxine Ramon), Am. J. Pub. Health **17**:1027, 1927.

that a negative Schick reaction may be taken as presumptive evidence of immunity to diphtheria but not as a guarantee of immunity.

It is obvious from an appraisal of the high percentages of negative Schick reactions in younger persons (tables 1, 2, 3 and 5) that only a few children continued to give a positive or a doubtful reaction after they had received three doses of toxoid. Furthermore, some of this small number gave a negative reaction later without having received an injection of toxoid after the first Schick test (table 7) and without having acquired clinical diphtheria in the interval between the two Schick tests. It would therefore appear to be safe and economically sound in a public health program in a large city to omit Schick testing for young children after, as well as before, active immunization to diphtheria by the administration of three doses of toxoid. Of course, with small groups, as in institutions or nurses' training schools, or in private practice, in which it may be desirable to pick out those persons, few as they are, who do not acquire sufficient immunity after receiving three injections of toxoid to give a negative reaction, and who require a further dose to render them so, the Schick test supplies the simplest method available for this purpose.

RESULTS OBTAINED

The data have been tabulated to show the relation of certain variables —age, sex, number of doses, size of doses, interval between doses and interval between the last dose and the Schick test—to the findings, as shown by Schick testing subsequent to injections of toxoid.

Table 1 shows the number in each age group tested for the first time at various intervals after the last dose of toxoid and the percentages found to react negatively among those who received two doses and among those who received three doses. It is apparent that the subgroups for each age and each interval are, in general, too small to form any reliable basis for determining the influence of these variables. But even in this detailed form, the figures are not without some value. Each age group among those given 3 doses of toxoid and tested from six to eleven months after the last dose is sufficiently large to yield significant results. The percentages found to react negatively in each age group at this interval of testing closely approximate the average of 96 per cent. In other words, the same degree of immunity, as revealed by and within the limits of the Schick test, was demonstrable in infants under 1 year, in children 1 year old and in older preschool and school children. While in the other divisions the numbers in the different age groups are small, there is nothing whatever in these data to suggest or to support the contention of Ramon and Debré [13] that younger children are not as readily immunized as older children, and though some of the

infants would probably have given a negative Schick reaction before the administration of toxoid, the long interval between the doses and the testing obviates, in great part, the necessity for considering the

TABLE 1.—*Percentage of Persons Giving a Negative Schick Reaction According to Dose and Age Interval Between Last Dose and Schick Test* *

Age in Years	Under 6 Mo.		6-11 Mo.		12-23 Mo.		2 Yr. and Over		Total	
	Number Tested	Percentage Sch.-ve	Number Tested	Percentage Sch.-ve	Number Tested	Percentage Sch.-ve	Number Tested	Percentage Sch.-ve	Number Tested	Percentage Sch.-ve
					Two Doses of Toxoid					
Under 1.....	2	100	13	92	3	100	11	73	30	87
1.....	12	100	80	89	27	89	58	83	178	87
2.....	6	100	40	85	26	85	41	78	113	83
3.....	6	84	31	94	13	85	29	76	80	85
4.....	2	50	25	92	10	100	21	95	58	95
5.....	3	100	33	91	19	100	18	78	73	90
6.....	4	75	12	100	7	72	11	82	34	85
7 and over....	..	..	9	89	2	100	..	..	11	91
Not stated....	2	100	5	80	5	100	..	..	20	75
Total.....	37	92	248	90	112	90	196	80	597	87
					Three Doses of Toxoid					
Under 1.....	106	99	753	95	52	94	16	88	929	96
1.....	163	97	1,150	97	112	92	77	81	1,506	96
2.....	52	95	464	97	43	98	26	100	586	97
3.....	35	95	329	97	32	94	27	82	425	96
4.....	29	100	244	94	19	100	17	88	310	94
5.....	19	95	227	99	22	91	11	82	279	97
6.....	15	100	128	94	12	92	8	88	163	94
7 and over....	26	89	245	96	9	89	8	87	288	94
Not stated....	12	92	65	99	12	92	5	80	94	96
Total.....	457	96	3,605	96	313	94	195	85	4,580	96

* Interval not stated: 2 doses, 4; 3 doses, 10.

TABLE 2.—*Percentage of Persons Giving a Negative Schick Reaction According to the Number of Doses and the Interval Between the Last Dose and the Schick Test*

Interval After Last Dose	2 Doses		3 Doses	
	Number Tested	Negative Reactions, Percentage	Number Tested	Negative Reactions, Percentage
Less than 6 months	37	92	457	96
6-11 months	248	90	3,605	96
12-23 months	112	90	313	94
2 years and over	196	80	195	85
Not stated	4	75	10	60
Total	597	87	4,580	96

passive immunity derived from the mother in these age groups.[20] With such slight reservations as should be made on account of this factor and more reasonable reservations on account of the limitations of the Schick

20. Fraser, D. T.: Studies in Diphtheria Immunity in Man, Tr. Roy. Soc. Canada (Sect. V) **28**:65, 1934.

test in measuring immunity, it is fair to conclude, therefore, that injections of toxoid may be administered at 6 months of age with the confident expectation of achieving as good immunization as at a later period.

Otherwise, the subgroups are, as stated, too small to consider individually, but the subtotals and totals, as well as table 2, demonstrate without question the decline in the ability to give a negative Schick reaction at the longer intervals before the test was done and the consistently higher degree of immunity induced by three doses as compared with two doses. Studies concerning the reversal from a negative to a positive Schick reaction and the possible progressive decline in immunity years after the administration of toxoid are being carried out.

TABLE 3.—*Percentage of Persons Giving a Negative Schick Reaction According to Dose, Age and Sex*

	2 Doses				3 Doses			
	Boys		Girls		Boys		Girls	
Age in Years	Number Tested	Negative Reactions, Per-centage	Number Tested	Negative Reactions, Per-centage	Number Tested	Negative Reactions, Per-centage	Number Tested	Negative Reactions, Per-centage
Under 1	14	79	16	94	503	95	426	96
1	76	88	102	86	771	95	735	96
2	41	90	72	79	306	98	280	96
3	35	89	45	82	210	96	215	95
4	25	88	33	97	157	95	153	93
5	31	90	42	90	145	97	134	98
6	17	77	17	94	79	91	84	96
7 and over	5	80	6	100	127	95	161	94
Not stated	15	73	5	80	48	98	46	94
Total	259	87	338	87	2,346	95	2,234	96

TABLE 4.—*Age Distribution by Sex* *

	Boys		Girls		Total	
Age in Years	Number	Percentage	Number	Percentage	Number	Percentage
Under 1	518	19.8	443	17.2	961	18.5
1	850	32.5	840	32.6	1,690	32.6
2	347	13.3	356	13.7	703	13.5
3	247	9.4	260	10.1	507	9.8
4	184	7.0	187	7.3	371	7.2
5	176	6.7	176	6.8	352	6.8
6	97	3.7	101	3.9	198	3.8
7+	132	5.2	167	6.4	299	5.6
Not stated	63	2.4	51	2.0	114	2.2
Total	2,614	100.0	2,581	100.0	5,195	100.0

* Data concerning 18 children who received four, five and six injections of toxoid before the Schick test are included in this table.

In table 3 the findings for the two sexes are shown. It is evident that sex is not a factor so far as the ability to give a negative Schick reaction after the administration of toxoid is concerned. The data also

support the conclusion arrived at in table 1 in regard to age and number of doses.

The age and sex distribution of the children treated are shown in table 4. The equality in the total number, with a slightly greater number of boys in the first year of life, is typical of what might be expected in such a random collection of children.[21]

In table 5 the data relating to the interval between the first and the last dose (immunizing interval) and the total amount of toxoid administered are shown. Again, the various subgroups are too small for comparative purposes. However, the group of 177 given 2 cc. in two

TABLE 5.—*Percentage of Persons Giving a Negative Reaction According to Immunizing Interval and Amount of Toxoid by Dose* *

Amount of Toxoid	Under 30 Days		30-65 Days		66-99 Days		100 Days and Over			
	Number Tested	Negative Reactions, Percentage	Number Tested	Negative Reactions, Percentage	Number Tested	Negative Reactions, Percentage	Number Tested	Negative Reactions, Percentage	Number Tested	Negative Reactions, Percentage
Two Doses										
1.0 cc.	13	85	6	83	..	..	1	100	21	86
1.5 cc.	15	80	10	60	..	..	..	..	26	73
2.0 cc.	177	92	67	93	9	89	9	89	263	92
Not stated	210	83	67	90	3	33	7	57	287	83
Total	415	87	150	89	12	75	17	76	597	87
Three Doses										
1.0 cc.	..	..	1	100	..	..	1	100	2	100
1.5 cc.	..	..	27	89	3	66	5	60	35	83
2.0 cc.	437	97	1,769	96	317	96	172	94	2,699	96
2.5 cc.	10	100	1,400	97	182	92	115	95	1,708	96
3.0 cc.	..	..	10	90	1	100	4	100	17	82
Not stated	5	100	88	95	9	100	10	80	119	91
Total	452	97	3,295	96	512	94	307	94	4,580	96

* Interval not stated: 2 doses, 3; 3 doses, 14.

doses in less than thirty days may be compared with the group of 437 given 2 cc. in three doses in less than thirty days. The group who received two doses showed 92 per cent with a negative Schick reaction and the group who received three doses, 97 per cent. The number of cases observed is small, but the result is in keeping with what might be reasonably anticipated. The practically complete agreement of the percentages of children found to have a negative Schick reaction when given 2 cc. in three doses in the various immunizing intervals shown is, with the limitations inherent in considering immunity as gaged by the Schick test, interesting and possibly instructive. At least, it can be

21. Vital Statistics, Canada, 1931, Dominion Bureau of Statistics, Ottawa, J. O. Patenaude, Printer to the King's Most Excellent Majesty, 1933.

said that so far as Schick testing shows the immunizing interval can be varied within fairly wide limits without interfering with the results. Among 1,769 children receiving three doses amounting to 2 cc. in from thirty to sixty-five days, 96 per cent were found to have a negative Schick reaction; among 67 children given the same amount in two doses in the same time, 93 per cent were found to have a negative reaction. The difference is in the direction anticipated, but the difference in the size of the groups invalidates comparison. A group of better size for comparison with the 1,769 children (given three doses amounting

TABLE 6.—*Result of First Schick Tests: Percentage Positive, Doubtful and Negative According to Dose and Age*

Age in Years	2 Doses				3 Doses			
	Number Tested	Percentage			Number Tested	Percentage		
		Positive	Doubtful	Negative		Positive	Doubtful	Negative
Under 1	30	10	3	87	929	3	1	96
1	178	11	2	87	1,506	3	1	96
2	113	16	1	83	586	2	1	97
3	80	15	..	85	425	3	1	96
4	58	5	..	95	310	4	2	94
5	73	6	4	90	279	3	..	97
6	34	15	..	85	163	4	2	94
7 and over	11	9	..	91	288	4	1	95
Not stated	20	20	5	75	94	4	..	96
Total	597	12	1	87	4,580	3	1	96

TABLE 7.—*Result of First Schick Test by Dose*

Schick Test, Doses	Positive		Doubtful		Negative		Total	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
2	71	11.8	9	1.5	517	86.7	597	100
3	139	3.0	59	1.3	4,382	95.7	4,580	100
4, 5 or 6	0	0.0	0	0.0	18	100.0	18	100
Total	210	4.0	68	1.3	4,917	94.7	5,195	100

to 2 cc. in from thirty to sixty-five days, of whom 96 per cent had negative Schick reactions) is that of 1,400 given 2.5 cc. in 3 doses in the same immunizing interval, of whom 97 per cent gave negative Schick reactions. The difference is, of course, hardly significant. With the reservations already emphasized, it is suggested that 2 cc. in three doses, as recommended by the Connaught Laboratories, is as satisfactory as the larger dose, of 2.5 cc.

Tables 6 and 7 are presented to demonstrate that neither age nor the number of doses was a significant factor in the ease or the difficulty encountered in reading the Schick reaction. In other words, "doubtful"

was not recorded more frequently at one age than at another, and, in fact, but 1 per cent of the total number of Schick reactions following either two or three doses were so recorded.

Table 8 shows that of 32 children who gave positive Schick reactions after two doses of toxoid and who were given one more dose of 1 cc., 31 gave a negative reaction when retested from four to six months later. Similarly, of 99 children who gave a positive Schick reaction after three doses and who were given an additional dose of 1 cc., 97 gave negative reactions when retested from four to six months later. One child given two doses and seven given three doses, who gave positive reactions but who were not given further toxoid, gave a negative reaction when retested later. This change may have been due to a variation inherent in the test, to the stimulus provided by the toxin injected

TABLE 8.—*Data Concerning 278 Children Whose Reaction to the First Schick Test Was Positive or Doubtful*

Additional Doses of Toxoid	Reaction to First Schick Test Positive or Doubtful	Second Schick Test		
		Negative	Positive	Not Done
	Two Doses Given Before the First Schick Test			
0	22	1	..	21
1	48	31	1	16
2	3	2	..	1
3 or 4	7	5	..	2
Total.....	80	39	1	40
	Three Doses Given Before the First Schick Test			
0	42	7	..	35
1	147	97	2	48
2 or 3	9	7	..	2
Total.....	198	111	2	85

when the first Schick test was done, as shown by Fraser and Halpern,[22] or to latent immunization from subclinical infection with the diphtheria bacillus.

CONCLUSIONS

1. Diphtheria toxoid administered to infants 6 months old achieves as good immunization, as gaged by the Schick test, as that administered to older children.

2. There is a decline in the ability to give a negative Schick reaction as the interval between the last dose of toxoid and the Schick test is prolonged.

3. A higher degree of immunity, as gaged by the Schick test, is induced by three doses than by two doses of toxoid.

22. Fraser, D. T., and Halpern, K. C.: Serial Titrations of Diphtheria Antitoxin Following Toxoid, Canad. Pub. Health J. **26**:476, 1935.

4. Three doses of toxoid amounting to 2 cc. give as satisfactory immunization as do three doses amounting to 2.5 cc., as shown by the Schick test.

5. Sex is not a factor so far as the negative Schick reaction following the administration of diphtheria toxoid is concerned.

6. The immunizing interval can be varied within fairly wide limits without interfering with the resulting immunity, so far as the Schick test shows.

Drs. D. T. Fraser and N. E. McKinnon, of the Connaught Laboratories, University of Toronto, made valuable comment on this work.

INFLUENCE OF TONSILLECTOMY ON RHEUMATIC INFECTION

RACHEL ASH, M.D.
PHILADELPHIA

Tonsillectomy is widely recommended for the prevention and the treatment of rheumatic infection. Kaiser,[1] whose statistical studies have helped to check the indiscriminate performance of tonsillectomy for unrelated conditions, expressed the belief that the effect on rheumatic infection warrants the routine removal of tonsils in all rheumatic children. Although he modified his earlier view as to the value of this procedure in preventing recurrences,[2] his investigations in Rochester, N. Y., led him to state that rheumatic infection not only occurs slightly more often among children with tonsils present but that there is a marked reduction in the mortality rate for children whose tonsils have been removed before the initial attack or subsequent to it.[3]

Not all clinical observers have been impressed with the value of tonsillectomy. Wilson, Lingg and Croxford,[4] after a review of preceding studies and an analysis of their own series of 413 cases of rheumatism in children, came to the conclusion that as recurrences of rheumatic manifestations are not prevented, routine removal of the tonsils for the prevention of rheumatic heart disease is not based on conclusive data. After making a detailed study of rheumatic and nonrheumatic children attending the outpatient department of two London hospitals, Campbell and Warner[5] decided that complete enucleation of the tonsils before the appearance of signs or symptoms of rheumatism did not prevent the onset of the disease, diminish its frequency

---

Read at the meeting of the Philadelphia Pediatric Society, March 9, 1937.

From the Department of Pediatrics of the University of Pennsylvania School of Medicine and the Children's Hospital.

1. Kaiser, A. D.: Children's Tonsils In or Out, Philadelphia, J. B. Lippincott Company, 1932.

2. Kaiser, A. D.: Incidence of Rheumatism, Chorea and Heart Disease in Tonsillectomized Children, J. A. M. A. **89**:2239 (Dec. 31) 1927.

3. Kaiser, A. D.: Influence of Tonsils on Rheumatic Infection in Children, J. Lab. & Clin. Med. **21**:609, 1936.

4. Wilson, M. G.; Lingg, C., and Croxford, G.: Tonsillectomy in Its Relation to the Prevention of Rheumatic Heart Disease, Am. Heart J. **4**:197, 1928.

5. Campbell, M., and Warner, E. C.: A Study of Rheumatic Disease in Children, Lancet **1**:61, 1930.

or lessen the incidence of rheumatic carditis. Wallace and Smith [6] suggested the possibility that early tonsillectomy may even increase the child's susceptibility. A higher incidence of acute rheumatism was noted in their group of 403 children on whom tonsillectomy had been performed before the age of 5 years than in the control group of 574 children whose tonsils had been removed during the later years of childhood.

In view of the conflicting published opinions, a study of the influence of tonsillectomy on the rheumatic children under the supervision of the Children's Hospital seemed advisable. Many of these children had been under continuous observation since 1922. Certain statistical factors pertaining to the group were published in a previous paper.[7]

For the present analysis there were chosen all the children with rheumatic infection who had come under observation in the ward or the cardiac disease clinic during the years from 1922 to 1936 with the exception of those whose illness began prior to 1922. The total number of these children was 532. In 11 cases no definite information could be obtained from the records as to the presence or absence of tonsils at the time of the original infection. In 96 (18.4 per cent) of the remaining 521 cases the tonsils had already been removed at the time of the first rheumatic manifestation; in 425 (81.6 per cent) they were still present.

INITIAL INFECTION

The average age at the onset of the infection in the cases in which tonsillectomy preceded the initial infection was 8.9 years, whereas in the cases in which the tonsils had not yet been removed the average age at the onset was 6.3 years, approximately two and one-half years less. The age at which tonsillectomy had been performed varied from 2 to 11 years, the average age being 5.8 years. The interval between the tonsillectomy and the onset of the infection varied from one month to eleven years, with an average interval of three and one-tenth years. In 15 cases the onset occurred within six months; in only 1 did it occur within one month, or at an interval which suggested that the disease had been precipitated in a susceptible person by the trauma of the operation.

The incidence of definite organic heart disease during the course of the initial infection varied only slightly in the two groups; it was 51.7 per cent in the group with tonsils and 49 per cent in the group

6. Wallace, H. L., and Smith, A. B.: The Effect of Early Tonsillectomy on the Incidence of Acute Rheumatism, Edinburgh M. J. **43**:452, 1936.

7. Ash, R.: Prognosis of Rheumatic Infection in Childhood: A Statistical Study, Am. J. Dis. Child. **52**:280 (Aug.) 1936.

without tonsils (table 1). The higher number of early deaths in the group with tonsils (5.6 per cent, as compared with 3.1 per cent in the other group) may be related to three factors other than the tonsils. More boys and more Negroes had not previously been operated on. It had previously been noted that among rheumatic children at the Children's Hospital more severe manifestations of the disease occurred in boys and in Negroes, despite their lessened tendency to

TABLE 1.—*Outcome of Initial Infection*

Tonsils	No.	Age at Onset, Yr.	Sex, Percentage		Race, Percentage		Valvular Heart Disease		Deaths	
			M	F	Negro	White	No.	%	No.	%
Removed before onset.....	96	8.9	34.4	65.6	15.6	84.4	47	49.1	3	3.1
Present at onset.....	425	6.3	45.4	54.6	18.6	81.4	220	51.7	24	5.6

TABLE 2.—*Influence of Age and Duration of the Illness on the Outcome When the Patient Survived the First Year*

	Tonsils Removed Before Onset			No Tonsillectomy			Tonsils Removed After Onset Within First Year			Tonsils Removed Subsequent to First Year		
Age at Onset, Yrs.	Number	Valvular Heart Disease, %	Deaths, %	Number	Valvular Heart Disease, %	Deaths, %	Number	Valvular Heart Disease, %	Deaths, %	Number	Valvular Heart Disease, %	Deaths, %
2- 4	2	100.0	0	11	63.6	27.2	26	50.0	19.2	27	63.0	18.1
5- 7	28	64.3	10.8	26	50.0	15.4	73	63.0	12.3	64	67.2	14.7
8-10	39	56.0	18.0	23	40.0	4.3	45	62.2	4.4	32	68.7	12.5
11-12	17	53.0	0.0	3	33.0	0	7	87.5	0	1	0	0
Duration After Onset, Yr.												
1- 4	42	47.6	0	32	31.3	0	46	45.6	0	36	58.3	0
5- 7	24	62.5	12.5	21	52.4	14.3	46	63.0	4.3	38	65.8	8.0
8-12	20	77.0	35.0	10	80.0	50.3	59	75.0	23.3	50	72.0	32.0

acquire the disease.[7] Moreover, the children whose tonsils had not been removed comprised a younger group. Higher death rates prevail for children taken ill early in life.[8] In the present study the high mortality for the younger children with tonsils is well exemplified (table 2).

Further evidence of the severity of the disease in younger children is the fact that in all the subdivisions of the groups studied, including the group whose tonsils had been removed before the onset of the

8. Findlay, Leonard: The Rheumatic Infection in Childhood, New York, William Wood & Company, 1932, p. 141.

disease, the average age at the time of the initial attack of the children that died was one or more years below that of each subdivision as a whole.

However, in the group tonsillectomized before the onset of the condition the age incidence was unlike that of the nontonsillectomized group (table 3). Whereas but 3.3 per cent of this group were taken ill at the ages of 2 and 3 years, 15.5 per cent of the nontonsillectomized group were attacked at those ages. In the latter group, the peak years of the onset of infection were from the fifth to the eighth, whereas the disease made its appearance most frequently from the seventh to the tenth year in children whose tonsils had been removed. The paucity of susceptible children at the lower age levels whose tonsils had been removed may account for the small number of such children affected.

TABLE 3.—*Initial Infection: Age Incidence in Children With and Without Tonsils*

	Tonsils Present		Tonsils Absent	
Age, Yr.	Number	Percentage of Total Group	Number	Percentage of Total Group
3	31	7.4	2	2.2
4	34	8.1	1	1.1
5	61	14.6	3	3.3
6	72	17.2	11	12.3
7	75	17.9	15	16.8
8	53	12.6	17	19.1
9	41	9.8	13	14.6
10	32	7.6	16	18.0
11	19	4.5	11	12.3
Total	418	100.0	89	100.0

An alternative explanation may be that tonsillectomy in the young child confers a certain degree of protection against rheumatic infection.

With the hope of obtaining information concerning the incidence of tonsillectomy in a control group of children belonging to families some member of which was under treatment in the wards or the outpatient department, the aid of the social credit worker of the Children's Hospital was enlisted.[9] Through her, during the course of routine consecutive interviews with parents, inquiries were made as to whether the children of the family had had their tonsils removed. In this way a random sample of 500 children between the ages of 3 and 11 years, with an average age of 6 years, was obtained. The tonsils of 32.8 per cent of this group had been removed. Since this operation had been performed before the onset of the infection on only 18.2 per cent of

9. Mrs. Eleanor Ferguson, social credit worker of the Children's Hospital, obtained the information concerning the incidence of tonsillectomy in the families receiving care at the Children's Hospital.

the rheumatic children, Kaiser's [3] finding that less than the expected number of tonsillectomized children are included in a rheumatic group at the time of the initial infection seems to be confirmed. However, the percentage of tonsillectomized children at each age level, when determined for the group taken at random, was found to decrease fairly sharply after the age of 8 rather than to rise progressively (table 4). Either the random sample chosen was not representative or there had been within recent years a marked increase in the number of tonsillectomies on young children. If the latter alternative were the case, the incidence of tonsillectomy in the group taken at random could not with accuracy be used as a standard for the group of rheumatic children, which had been assembled over a period of fourteen years. If one accepts the figures for the control group, tonsillectomy seems to lessen the tendency of the young child to acquire the disease but to increase

TABLE 4.—*Relation of Tonsillectomy to Age*

Age, Yr.	Control Group		Rheumatic Group	
	Number	Tonsils Absent, %	Number	Tonsils Absent at Onset, %
3	64	28.0	33	6.0
4	61	32.8	35	3.1
5	80	36.3	64	4.7
6	77	36.3	83	13.2
7	63	41.3	90	16.6
8	50	30.0	70	24.3
9	36	28.0	54	24.0
10	34	33.0	48	33.0
11	35	20.0	30	36.0
Total	500	32.8	507	18.2

the susceptibility of the child over 10. Moreover, tonsillectomy seems to decrease the mortality among children taken ill before the age of 8 but to increase it during the next three years of life (table 2).

FATE OF THE SURVIVORS OF THE FIRST YEAR OF ILLNESS

After recovery from the first attack, 37 children had been ill for a total period of less than one year or could not be traced. There were left 450 children, 86 of whom had become ill after a tonsillectomy was performed. The further course of these two groups of survivors of the first year of illness was traced.

When the two groups were considered as a whole, no significant difference in the incidence of valvular heart disease and of deaths was found (table 5). After an average duration of 5.2 years, 60 per cent of the 86 children on whom tonsillectomy had been performed before the onset of the disease had acquired valvular heart disease and 11.6 per cent had died. After an average duration of 6.4 years, 58.6 per cent of the 364 children with tonsils present at the onset had acquired

valvular heart disease and 12.3 per cent had died. When one included the cases in which the disease was fulminating, the death rate for the 89 children with tonsils removed before the onset was 14.6 per cent, as compared with 18 per cent for the 388 children with tonsils present, a difference of no importance when one takes into consideration the fact that the latter group was a younger group containing a higher percentage of boys and of Negroes and that it had had an additional year of illness. In table 2 the marked influence of the duration of the infection on the mortality rate of all groups is outlined.

EARLY VERSUS LATE TONSILLECTOMY

If tonsillectomy is of value in the treatment of the rheumatic child, it is important to know at what phase of the disease the operation is

TABLE 5.—*Outcome When Patient Survived the First Year*

Tonsils at Onset	Number	Age at Onset, Yr.	Duration, Yr.	Initial Infection: Rheumatism, %*	Initial Infection: Chorea, %	Initial Infection: Carditis, %	Chorea Only, %	Boys, %	Negroes, %	Heart Disease: Number	Heart Disease: Percentage	Deaths: Number	Deaths: Percentage
Removed	86	8.9	5.2	67.4	22.1	10.5	10.4	31.4	16.3	51	60.0	10	11.6
Present	364	7.0	6.4	70.4	20.3	9.3	12.9	45.0	18.4	213	58.6	46	12.3
No tonsillectomy	63	6.6	4.7	76.2	17.4	6.4	4.7	44.4	38.1	30	47.6	8	12.7
Early tonsillectomy	152	6.7	6.6	69.7	19.8	10.5	13.1	47.3	11.1	94	62.6	16	10.5
Late tonsillectomy	124	6.2	6.8	71.8	18.4	9.8	11.2	44.6	12.8	83	66.4	19	15.3
Unknown	25	7.5	7.8	52.0	40.0	8.0	40.0	40.0	36.0	6	24.0	3	12.0

* Rheumatism includes pains in the joints and arthritis and fever of varying degree with or without associated heart disease.

indicated. Some authorities believe that tonsillectomy should be performed early, even in the presence of acute signs and symptoms. It has been argued that since one does not hesitate to remove an acutely inflamed appendix, one should not hesitate to remove tonsils, which may be the primary focus of existent rheumatic infection.

An attempt was made to determine whether the length of time between the onset of the infection and the removal of the tonsils influenced the outcome. Over a period of fourteen years these rheumatic children had been under the care of nine different medical chiefs, including the directing physicians in the wards and the clinic, representing various points of view as to the most advisable time for tonsillectomy. As a result, in some instances tonsils were removed while the infection was still active, either early in the first attack or during a subsequent recrudescence, while in others the operation was performed only in an interval free from laboratory or clinical signs of active infection. In 155 cases the tonsils were removed during the

first year, between one and eleven months from the onset, the average interval being four and one-half months, whereas in 124 cases tonsillectomy was performed subsequent to the first year, between fourteen months and eleven years from the onset, the average interval being two and eight-tenths years. In addition, in 63 cases in which the child survived the first year of illness the tonsils had never been removed, and in 25 cases no accurate information could be obtained as to the date of subsequent removal.

When one attempted to analyze these groups their lack of homogeneity at once became apparent. There is probably no method of classifying patients ill with rheumatism, influenced as this disease is by so many variable factors, by which one can assemble groups with no initial difference in composition. For this reason only large differences in results can be considered significant.

In the present series (table 5) a large proportion of children whose tonsils had never been removed suffered from infection of recent origin (average duration, four and seven-tenths years). This fact, together with the fact that a certain number with mild attacks, for whom tonsillectomy had not seemed urgent, were included, may explain the low incidence of cardiac involvement. However, also not operated on were a small number of children with severe infection for whom the risk of tonsillectomy had never been taken. These children were responsible for the fact that the death rate was disproportionate to the extent of the cardiac damage. The incidence of Negroes was high in this group (38 per cent) and was still higher among those that died (50 per cent). At first glance the group in which tonsillectomy was performed early seemed to bear a close resemblance to that in which the operation was deferred. On closer inspection, however, it became evident that in the latter group the children at the onset were six months younger, their illness had lasted three months longer, there were fewer instances of "pure chorea," the death rate of which is negligible, and there were a few more Negroes. The only difference in favor of the group subjected to early operation was the lower percentage of boys. In clinical composition the difference was even more marked. Included in the group operated on after the first year was a relatively high proportion of children with severe persistent infection prolonged into the second year, concerning whom a certain amount of caution had been exercised, whereas in the group with tonsils removed early there was a higher percentage of children with uneventful, early subsidence of the first attack. Although the mortality rate was lowest in the group in which tonsillectomy had been performed before the expiration of the first year, in view of the difference in composition of the two groups one hesitates to ascribe too much significance to these figures. The death rate of the combined group of children whose tonsils had been removed

after the appearance of rheumatic manifestations was 12.6 per cent—differing little from that of the group in which the tonsils remained intact (12.7 per cent) or from that of the group in which the tonsils had been removed before the onset (11.6 per cent).

A separate analysis of the children whose tonsils had been removed incompletely was not attempted. In previous observations on rheumatic children reported by others,[10] it had been found that the results in children on whom complete enucleation had not been performed did not differ from those in the tonsillectomized group as a whole. On the other hand, Campbell and Warner[5] reported that incomplete enucleation was followed by an increased tendency to acquire rheumatism.

REACTIONS TO TONSILLECTOMY

Reactions following rapidly on tonsillectomy predominated in the group in which the operation was performed early in the course of the disease. After such early operations, reactions were recorded in 18 cases (11.8 per cent), whereas reactions were noted subsequent to the first year in only 3, in all of which there was evidence of active infection at the time the operation was performed. Only manifestations occurring within a period of less than three weeks after the operation were considered. Eleven children had flare-ups of carditis; in 3 cases death resulted. An exacerbation of chorea followed the operation in 4 cases. Prolonged febrile attacks were noted in 4, and pains in the joints and fever, in 2. In addition, there were 3 cases of severe postoperative hemorrhage. Undoubtedly many reactions were not recorded, since children frequently were discharged within a few days after operation or were operated on in other hospitals.

The following case is an example of carditis terminating in death after tonsillectomy early in the course of rheumatic infection.

F. D., an Italian girl 5 years of age, was taken ill in November 1924 with rheumatic fever. She was treated at home under the care of her family physician until Jan. 7, 1925, when she was admitted to the Children's Hospital. A few days before her admission both ankles had again become swollen and painful. On admission these manifestations had subsided. The child's general condition was good. The heart was only slightly enlarged; an apical systolic blow was present. After the first two days the temperature curve was stable until the time of her tonsillectomy. This operation was performed on January 30, preparatory to admission to the Children's Heart Hospital. Immediately after the operation the temperature rose to 102 F.; it remained at this level for five days, reaching normal on February 6. After a symptomless interval of eleven days, on February 18 there was a sudden rise in the temperature and the pulse rate, associated with a rapid and marked increase in cardiac dulness. On February 22 a pericardial

10. Wilson, Lingg and Croxford.[4] Wallace and Smith.[6]

friction rub was noted; this persisted until death, on March 3, approximately four months after the onset of rheumatic infection and five weeks after the tonsillectomy.

On the other hand, tonsillectomy during an active phase did not always provoke a rheumatic exacerbation. When one considers the many spontaneous relapses during the early months of rheumatic infection it is perhaps unfair to lay too much stress on the preponderance of such relapses following early tonsillectomy. The observation of repeated severe reactions following immediately on tonsillectomy, however, would suggest the need for caution. The present policy of the cardiac disease clinic of the Children's Hospital is to advise operation, if at all, only when both the temperature and the sedimentation rate of the erythrocytes are normal. No rheumatic exacerbation has yet followed an operation performed under such precautions.

It may be of interest to note that besides these reactions following tonsillectomy, there occurred after the extraction of a tooth one instance

TABLE 6.—*Incidence of Single Attacks in the Survivors of the Second Year*

Tonsils	Number	Single Attacks	
		Number	Percentage
Absent at onset	77	18	23.4
Never removed	49	10	20.4
Removed within first year	137	34	24.8
Removed after first year	122	18	15.4
Present at onset—total	308	62	20.1

of hemorrhagic nephritis, one recrudescence of rheumatic fever and three attacks of chorea.

RECURRENCES

No favorable influence on recurrences was noted following tonsillectomy. Such rheumatic manifestations as arthritis, carditis, pains in the joints, recurrent epistaxis and chorea occurred within one or more years in 67 per cent of the children operated on. The incidence of single attacks without subsequent manifestations among those in whom the disease had existed at least two years was found to be small in all groups (table 6). Since the outcome of rheumatic infection is largely dependent on the extent of recurrences, it is difficult to see how a procedure which has no marked favorable effect on recurrences can influence the evolution of cardiac lesions or the death rate.

That the removal of tonsils in the younger brothers and sisters of a rheumatic child will not necessarily prevent infection is demonstrated by the following case.

M. B., an Italian girl born in 1915, acquired chorea at the age of 10 years. The heart remained normal during this attack. Immediately after recovery,

approximately four months from the onset, the tonsils were removed uneventfully. In the spring of 1932, at the age of 17, she experienced an attack of rheumatic fever, which left her with a damaged mitral valve.

T. B., the brother of M. B., born in 1918, underwent a tonsillectomy at the age of 8 years. Three years later, at the age of 11, he acquired chorea. When he was admitted to the Children's Hospital six weeks after the onset, signs of mitral regurgitation were noted. Shortly after his admission an attack of acute abdominal pain associated with marked rigidity of the right rectus muscle occurred. An operation was performed, but no evidence of acute appendicitis was found. The recovery was uneventful. In 1935, when a follow-up examination was made, mitral disease was still present.

A. B., the third child in this family, born in 1925, had her tonsils removed at the age of 4 years. In January 1933, at the age of 7 she acquired chorea, and she recovered from that attack with no cardiac damage. During the succeeding six months, however, she suffered two relapses of chorea; these were associated with signs of mitral disease, which were still evident in 1934.

Of the entire series of 532 children, 5 died of subacute bacterial endocarditis. In four of these children the tonsils had been removed from one month to two years after the onset, the interval averaging eleven months. The average period from the onset of rheumatic infection to death was five and one-half years. Tonsillectomy seems to be of small value in preventing the development of subacute bacterial endocarditis.

COMMENT

Whether the tonsillar tissue serves as the initial site of entry and the permanent focus for the etiologic agent of rheumatism or whether tonsillitis when it occurs with rheumatic fever is merely a part of a generalized infection is a debatable subject. Certainly rheumatic fever may occur in a person whose tonsils have been enucleated or in whom acute tonsillar involvement is not evident at the time of the primary attack. Kaiser pointed out that although tonsillitis is a common infection in approximately 35 per cent of all the school children in Rochester, the incidence of all types of rheumatic infection is less than 8 per cent and that of rheumatic heart disease less than 2 per cent. Not infrequently an acute rheumatic manifestation will have been preceded at an interval of one or two weeks by acute tonsillitis or infection of the upper respiratory tract. More frequently still, sore throats or colds even in the rheumatic child are followed by no rheumatic symptoms. According to Coburn,[11] only infections due to a special toxin-producing hemolytic streptococcus to which the susceptible person responds by delayed formation of antibodies are followed by the appearance of rheumatic symptoms. Schlesinger [12] also linked infections due to hemo-

11. Coburn, A. F.: Observations on the Mechanism of Rheumatic Fever, Lancet **2**:1025, 1936.

12. Schlesinger, B., and Signy, A. G.: Further Studies of the Etiology of Acute Rheumatism, Lancet **1**:1090, 1935.

lytic streptococci to the appearance of rheumatic manifestations, but he assumes that in some way recovery from such infections renders the organism vulnerable to the yet undiscovered cause of rheumatism, which in his opinion may well be a virus.

Assuming that the tonsils serve as a focus of attraction for such predisposing infections, Kaiser postulated that their removal may produce three results: (1) reduction in the incidence of rheumatic infection among children who have never been subject to the disease, (2) prevention of recurrences in children already attacked and (3) lowering of the mortality rate.

In Rochester [8] the incidence of rheumatic disease among tonsillectomized children was found to be less than the expected incidence. There is some doubt as to whether the two groups considered were strictly comparable. The nontonsillectomized group consisted of school children whose parents refused to permit an operation advised by the examining physician. The tonsillectomized group, therefore, was composed of children whose parents were willing to permit the advised operation. The factor of parental neglect may be an important one in the nontonsillectomized group. Only the children of singularly indifferent parents could attain high school age with diseased tonsils still present. Actually, since tonsillectomy is advised as a matter of routine in the United States for rheumatic infection, one would expect to find a higher incidence of rheumatism in a tonsillectomized group. Such was the case among the populace of Hagerstown, Md.,[13] and among the entering students of the University of California.[14]

Furthermore, it does not seem that a city-wide incidence of tonsillectomy can be applied as a standard to a group of rheumatic children most of whom come from the underprivileged classes. Many more children have their tonsils removed in the families at the higher economic levels. At outpatient departments in London [5] and in Edinburgh [6] no lessening in the incidence of rheumatism was noted among tonsillectomized children.

However, even if no doubt existed as to the value of tonsillectomy in the prevention of rheumatism, the problem would not be solved. In the present series the average age at the time of the initial attack of the children with tonsils present was 6.3 years. Since there is some evidence to indicate that tonsils have a physiologic or immunologic value in early life, few physicians would care to recommend routine tonsillectomy before the age of 6 years. Nor would removal

13. Collins, S. D., and Sydenstricker, E.: Epidemiologic and Statistical Study of Tonsillitis, Bulletin 175, United States Treasury Department, Public Health Service, 1928.

14. Cunningham, R. L.: Normal, Absent and Pathologic Tonsils in Young Women: A Comparison of Histories, Arch. Int. Med. **47**:513 (April) 1931.

of none but diseased tonsils be the solution. Campbell and Warner [5] found no more evidence of diseased tonsils in rheumatic children than in nonrheumatic children.

More important is the question of the value of tonsillectomy in the case of the child already subject to rheumatism. In this and all previous studies it has been shown that tonsillectomy has no influence on recurrences. Since this is true, it is difficult to see how tonsillectomy can exert any favorable influence on the future course of the disease or on the death rate.

In the present series there was no significant difference between the death rate for the children with tonsils absent at the onset and that for the children whose tonsils were removed subsequently or never removed, due consideration being paid to the variable statistical factors for each group. For the children whose tonsils were removed early in the course of the disease the death rate was somewhat lower than for those whose operation was deferred. There is some doubt as to the significance of this variation, in view of the difference in composition of the two groups. There is no doubt as to the high incidence of rheumatic exacerbations following early operation.

How can one reconcile these conclusions with those derived by Kaiser [3] from his investigations at Rochester, where the mortality rate was found to be approximately 50 per cent less for children whose tonsils had been removed before the initial attack? Perhaps the difference rests in the interpretation of the figures obtained in that city. The children were divided into three main groups: (1) those whose tonsils remained, for whom the death rate was 13 per cent; (2) those whose tonsils had been removed before the initial attack, for whom the death rate was 7 per cent, and (3) those whose tonsils were removed after the initial attack, for whom the death rate was 4 per cent. Seemingly, all the early deaths were debited to the first and second groups, whereas in the third group were placed only the survivors whose tonsils were removed subsequently. It would seem fairer to compare the outcome in cases in which the tonsils were present at the time of the initial attack with that in cases in which they were not and to note the influence of tonsillectomy on the survivors in all groups. With such a method of analysis, the death rates for the three groups observed in Rochester would probably have approximated each other, but since no figures for early deaths have been published one cannot be sure.

Consideration of the results in the series of rheumatic children whose cases are analyzed in the present paper leads to the belief that tonsillectomy in itself does not appreciably influence the future course of rheumatic infection. There is no justification, therefore, for the

routine performance of this operation. It should be advised only when there is a definite history of recurrent tonsillar infection or evidence of disease within the tonsils. It should be performed only after careful observation of the individual child and at a stage when the disease is quiescent.

SUMMARY

An analysis is made of the effect of tonsillectomy on the course of rheumatic infection in 522 children treated at the Children's Hospital between 1922 and 1936.

Tonsillectomy did not prevent recurrences of rheumatic manifestations.

Neither the presence or the absence of tonsils at the time of the initial infection nor the removal of tonsils subsequent to the onset had any demonstrable influence on the incidence of cardiac involvement or the death rate, due consideration being paid to the associated variable statistical factors.

A high incidence of rheumatic exacerbations followed immediately on tonsillectomy performed early in the course of the disease.

Tonsillectomy for the rheumatic child seems to be indicated only when there is definite evidence of disease in the tonsils and not as a routine procedure. The operation should be performed only during an inactive phase of the infection. Associated with the absence of other symptoms, the combination of a normal temperature curve and a normal sedimentation rate of the erythrocytes may be taken as indications of an inactive phase.

NOTE.—Since this paper was submitted for publication Dr. Milton Rapoport has applied the chi-square formula to the following sets of figures: (1) deaths as a result of the initial infection among children with tonsils present or absent at the onset, (2) deaths in these two groups among the survivors of the first year of illness and (3) deaths in the group in which tonsillectomy was performed early in the course of the disease, as compared with those in the group in which tonsillectomy was deferred. His findings were that none of the differences noted were statistically important, i. e., they were no greater than the chance difference that might arise in any two groups of the size compared. This seems to furnish the final argument to support the conclusion that in this group of rheumatic children observed in Philadelphia tonsillectomy could not be shown to influence the outcome of rheumatic infection.

5636 Pine Street.

DISCUSSION

DR. D. STEWART POLK: I should like to compliment Dr. Ash on her careful and thoughtful work. She has done all the statistical and also most of the clinical work. I think it is a fine piece of work. It seems that her study of the effect of serum gives one nothing to be cheerful about. In other words, it seems that specific therapy in rheumatism is lacking. Streptococcic products have been tried out intravenously; also, streptococcus antitoxin; now polyvalent human serum has been tried out and has been ineffective; so, if one is looking for a specific treatment for rheumatism one has to look further.

The clinical impression of many pediatricians now is that the closest one can get to specific treatment is in using transfusions of whole blood fairly frequently —two small transfusions a week, which can be given from one drawing of blood. This treatment should be continued until the blood picture approaches normal. It has been noted by a number of observers that when the red blood cell count and hemoglobin content become approximately normal the signs of rheumatism in most cases disappear. There seems to be a large percentage of patients that are making some progress who make progress faster when the transfusions are given frequently. Perhaps one has something here that one can use as more or less specific though not etiologically specific.

Tonsillectomy is a very debatable subject, and Dr. Ash has brought out a number of points to the effect that tonsillectomy is not all that it has been thought to be in the treatment of rheumatism. About the only thing that can be assumed is that early tonsillectomy may be of some value in postponing an attack of rheumatism if done before 6 years of age and not many doctors are going to require that of patients. As Dr. Ash pointed out, the most dangerous time to take out the tonsils is shortly after the onset of rheumatic infection. Dr. Jones, of Boston, pointed out that tonsillectomy or any other operation is very apt to produce a recurrence of rheumatism. Recurrences of carditis are frequent during the first year, when rheumatic recurrences are most likely. As Dr. Ash pointed out, there were three deaths closely associated with tonsillectomy—occurring so soon after tonsillectomy as to incriminate the operation as having been done at the wrong time. Tonsillectomy probably never should have been done at all. The advantage of tonsillectomy, if any, is demonstrable only if the operation is done before the age of 6 years and before the age of onset of rheumatism.

Still the consensus is that foci of infection of all sorts should be removed, and certainly the tonsils in many rheumatic children are foci of infection. The teeth and sinuses are also foci of infection, and one has to pay attention to all of them. If tonsillectomy is to be done, the time has to be chosen with great care as to season; preferably it should be done in the warmer months, at a time when the patient is in the best possible condition and when the rheumatism is definitely quiescent, and for that one needs negative clinical and laboratory signs, and probably a sedimentation rate of 10 or less. It is also important that the patient and all contacts of the patient should be free from infection of the respiratory tract, or throat infection may follow closely on tonsillectomy.

Tonsillectomy is of no particular value in the treatment of chorea, and chorea has a relatively small influence on the incidence of rheumatic heart disease. Chorea is made worse by the trauma of tonsillectomy. It seems that tonsillectomy, if it is to be done at all, should be reserved until the chorea has been quiescent for some time.

Dr. O. F. Hedley: My colleagues and I are grateful to Dr. Ash for the thoughtful paper presented. This type of research on rheumatic fever is badly needed. It is hoped that her conclusions will be borne out by an even larger statistical series.

At the Children's Heart Hospital we have been able to corroborate partially a number of Dr. Ash's statements. The disease appears to be much more serious in boys than in girls. Throughout this winter we have had considerably more difficulty in managing the boys. We receive them much later as a rule than the girls. Furthermore, they are inclined to be physically active and not as amenable to treatment.

There is much to be said on both sides with regard to the question of compulsory tonsillectomy for admission to the Children's Heart Hospital. I am no enthusiast over 100 per cent rulings of any sort. It is much better to consider each case on its merit. Nevertheless, there are some factors in the physical set-up of the Children's Heart Hospital which should be taken into consideration. The hospital consists of two open wards with very poor facilities for isolating patients with intercurrent infections. Patients with severe complications would have to be sent back to the hospital from which they came. This would be inconvenient for all.

Furthermore, there are no provisions at the Children's Heart Hospital for performing tonsillectomy. For these reasons I believe we should be slow in making changes.

An examination of the records of the last 50 patients admitted revealed an average interval of nineteen months between the first attack of rheumatic fever and the first admission to the hospital. For the boys the interval was twenty-one months and for the girls seventeen months.

Of the 50 children only 6 were admitted within six months after the first attack of rheumatic infection; 6 were admitted within a year; 6, between one and two years; 7, between three and four years; 2, between four and five years; 2, between five and six years, and 1, more than seven years after the first attack. In 7 instances it was impossible to determine when the child had the first attack of rheumatic infection—in these the condition was probably of long standing.

Of the 16 children admitted with rheumatic infection of less than eighteen months' duration, 9 had been tonsillectomized before the occurrence of rheumatic fever. This tends to bear out Dr. Ash's view concerning the lack of value of tonsillectomy as a preventive measure. That leaves us with 7 patients on whom tonsillectomy was done between the attack of rheumatic fever and admission to the Children's Heart Hospital. Of these 7 patients, 5 had histories of tonsillitis and probably should have had their tonsils taken out. This leaves only 2 of 16 children with early admission to the hospital on whom tonsillectomy may have been performed needlessly.

I see comparatively few clean throats. This does not mean that the tonsils have not been taken out satisfactorily. It means that by the time rheumatic infection has developed these youngsters have begun to show considerable lymphoid hyperplasia and to all intents and purposes have additional tonsillar tissue.

Unfortunately almost all observations in hospitals are made on persons of the lower social strata. It is perfectly possible that had thoracic surgery for tuberculosis been first practiced solely on Negroes, and another group of Negroes used as controls, a very poor impression of its value would have been obtained. I wonder if a similar factor enters into many of the statistics dealing with rheumatism. The children with rheumatism are reared in very destitute surroundings, admitted to the hospital after very severe infection and then go back to their homes to live again in a very poor environment. It seems questionable whether tonsillectomy or any other single therapeutic measure can overcome such a handicap. Before condemning tonsillectomy as a preventive measure it may be well to study its influence on children subjected to better home care and more constant medical supervision.

DR. HYMAN I. GOLDSTEIN: May I ask whether it is not a fact that various forms of acute tonsillitis are more frequently met with in these children? Are these rheumatic children more susceptible to the various forms of tonsillitis? Do you consider follicular tonsillitis or similar forms of tonsillitis contagious?

DR. RACHEL ASH: Dr. Polk mentioned the use of repeated small transfusions in the treatment of rheumatic fever. Such transfusions combat the anemia which is so prominent a symptom in patients with rheumatic infection. We feel that a single large transfusion often does harm but that repeated small transfusions seem to hasten recovery in the child who is progressing favorably. However, they do not seem to have any influence on the child with a protracted, polycyclic form of infection.

Perhaps I misunderstood a statement made during the discussion, but I wish to make it clear that in the present series tonsillectomy could not be shown to exert any favorable influence on rheumatic infection no matter when it was performed.

It is fairly obvious that the Children's Heart Hospital receives so few children with rheumatic infection in an early stage largely because of the ruling that the tonsils must be removed before admission. In the present series, 2 of the 3 deaths following tonsillectomy occurred in children on whom the operation was performed early in the course of the disease merely in order that they might be sent to that

hospital. It is our policy now to remove tonsils only when the infection is inactive and the sedimentation rate of erythrocytes normal. It sometimes takes two or three years for this stage to be reached.

To wish for a group of 500 rheumatic children among well-to-do families concentrated in one locality is almost to wish for the impossible, for it is the underprivileged child who acquires rheumatic infection. Is the rheumatic child more susceptible to tonsillitis? I do not think so. Moreover, many children have sore throats, but relatively few of these children acquire rheumatic infection.

We do not feel that the data obtained in the present study prove that children receiving injections of lyophile serum are thereby protected against colds, but the fact that the average number of colds in the group receiving serum was less than that in the control group is suggestive. Such protection is transitory only and is due to the passive transference of antibodies. Our injections were given once a month.

ROLE OF ADVANCED MATERNAL AGE IN CAUSING MONGOLISM

A STUDY OF 2,822 CASES

ADRIEN BLEYER, M.D.
ST. LOUIS

Although mongolism is now in its ninety-first year as a medical subject,[1] its origin remains obscure. More than a score of theories have been proposed to explain it; among them is the idea that the ages of the parents may in some way be responsible. For example, the parents may have been too old or too young at the birth of the child; a great discrepancy may exist between their ages; the child may be a first-born, subject to all the well known hazards of that birth position, or he may be the last-born after a long line of pregnancies. Again, a long interval preceding birth has been thought a cause; in this case the afflicted child appears after a period of reduced and perhaps defective fertility. This has brought up another factor, namely, the possible relation of low fertility in certain women to mongolism. Lastly, there is the time-honored theory of reproductive exhaustion, especially of the mother. Thus the age of the parents is not a single factor, but a group of factors which may to advantage be studied individually. They are placed together in this list:

1. Advanced maternal age
2. Advanced paternal age
3. Immaturity of either parent
4. Primogeniture (the mongoloid imbecile the first-born child)
5. A broad difference in the ages of the parents
6. A prolonged interval preceding the birth of the child afflicted with mongolism
7. Reproductive exhaustion from a long line of pregnancies, as revealed by study of the order of birth

---

Read at a meeting of the American Association on Mental Deficiency, Atlantic City, N. J., May 6, 1937, by invitation.

From the Pediatric Department of the Washington University School of Medicine and the St. Louis Children's Hospital.

1. Seguin, E.: Le traitement moral, l'hygiène et l'éducation des idiots, Paris, J. B. Ballière, 1846.

8. The supposedly low fertility of women producing children with mongolism
9. Ultimogeniture (the mongoloid imbecile the last-born child)
10. Paternal reproductive exhaustion

Great confusion has arisen because of the interlocking of these factors and because of the difficulty of studying them separately.

ADVANCED MATERNAL AGE

I shall not review the literature relating to the influence of advanced maternal age in causing mongolism other than to state that the writers are divided into three groups. The oldest and, I believe, the most interesting of these is the affirmative group, in which are found such distinguished leaders as Shuttleworth,[2] Jenkins[3] and Penrose.[4] In the second, the negative, group are found the eminent contributors Macklin,[5] Whitney[6] and Wile and Orgel;[7] and in the third group, consisting of those who neither agree nor disagree but entertain a dubious attitude, are found two eminent writers, Goddard[8] and Brousseau.[9]

It was the purpose of the present study to secure data on a group of cases which would reduce the likelihood of error in proportion to its size and which would be large enough to make unnecessary the use of the expectancy calculations used in interpreting data on smaller groups.

The Year Book of the American Association on Mental Deficiency was consulted, and letters were sent to members connected with institutions for the mentally defective throughout the country. There were 122 of these letters, a form being enclosed covering the ages of the parents and the birth rank of the persons showing mongolism. Preparing and sending in all this material entailed a great deal of time and

2. Shuttleworth, G.: Mongolian Imbecility, Brit. M. J. **2**:661, 1909.

3. Jenkins, R. L.: Etiology of Mongolism, Am. J. Dis. Child. **45**:506 (March) 1933.

4. Penrose, L. S.: (*a*) The Relative Effects of Paternal and Maternal Age in Mongolism, J. Genetics **27**:219, 1933; (*b*) The Relative Aetiological Importance of Birth Order and Maternal Age in Mongolism, Proc. Roy. Soc., London, s.B **115**:431 (Aug. 1) 1934; (*c*) A Method of Separating the Relative Effects of Birth Order and Maternal Age, with Special Reference to Mongolian Imbecility, Ann. Eugenics **6**:108, 1934.

5. Macklin, Madge Thurlow: The Manner of Inheritance of Mongolism, Am. J. M. Sc. **178**:315, 1929.

6. Whitney, E. A.; Shick, M. M.; Bedrossian, E., and Whitney, S. P.: A General Review of Mongolism with Study of Cases at Elwyn Training School, M. J. & Rec. **132**:80 (July 16) 1930.

7. Wile, I. S., and Orgel, S. Z.: A Genetic Study of Mongolism, M. J. & Rec. **127**:431 (April 18) 1928.

8. Goddard, H. H.: Feeblemindedness: Its Causes and Consequences, New York, The Macmillan Company, 1914.

9. Brousseau, Kate: Mongolism, New York, The Macmillan Company, 1928.

effort on the part of a great many indulgent persons. Replies were received from 115 institutions; 60 correspondents reported cases, providing the desired information about 2,196 mongoloid imbeciles. A second letter was then sent to the secretaries of the various state boards of health, which brought in a list of 27 additional institutions, from which data on a few more cases were secured. It is felt that the information on the majority of the mongoloid imbeciles in the institutions of this country and of Canada is included in this report.

Special help was given by Dr. R. L. Jenkins, who sent the original Brushfield histories of 201 cases as well as 163 histories from his own

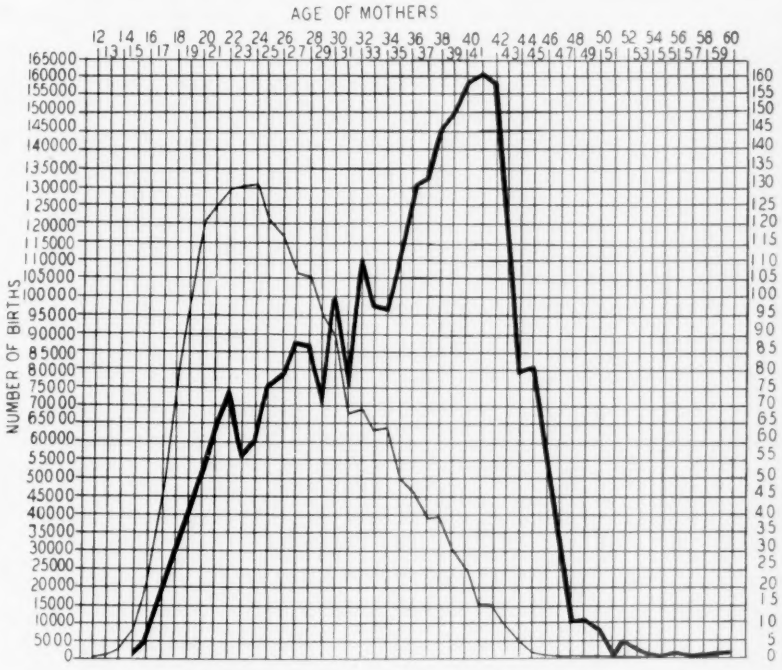

Chart 1.—Maternal age at the birth of 2,822 mongoloid imbeciles compared with maternal age at the birth of about 2,000,000 children in the United States in the year 1934 (exclusive of Massachusetts and New Hampshire). This shows the tendency of the mongoloid imbecile to be born of an old mother. The peak maternal age in the general population is 24 years; in the group producing mongoloid imbeciles it is 41 years.

service at the Institute for Juvenile Research in Chicago. To these were added 217 histories compiled by Penrose in England and 95 compiled by Comby in France. The remaining data were collected locally, bringing the group of cases studied to slightly over 2,800, about 200 cases having been discarded because of insufficient data.

A compilation of these reports is summarized in chart 1. The finer line to the left indicates the normal ages of fecundity of American women

in the year 1934 and includes all births in the United States (exclusive of Massachusetts and New Hampshire) for that year; it represents over 2,000,000 births and was made from figures prepared at the Bureau of the Census under the direction of the chief statistician, Dr. Halbert Dunn. In this line is seen the peak age of fecundity, which is 24; the rate of child bearing declines sharply after the age of 30, only 26.7 per cent of all babies being born after that age. To the right, shown in a heavier line, are the belated births of the children afflicted with mongolism; their number becomes impressive as fecundity approaches the vanishing point, the peak year being the forty-first. Sixty-eight and one-tenth per cent of the children with mongolism were born to women more than 30 years old, during an age period which produces less than 27 per cent of all births in the United States. Of the entire group of 2,822 mongoloid imbeciles, 900 were born to women under 31 years of age and 1,922 to women from 31 to 60 years of age.

Needless to say, this distribution of births is altogether abnormal, indicating that the determining factor in mongolism is age: The mongoloid imbecile is usually born of an old mother, and the old mother is a prolific producer of mongoloid imbeciles.

It then became interesting to see whether one might detect in these figures the point at which advancing maternal age begins to operate. To this end the ages of the mothers at the births of the mongoloid imbeciles were set out in quinquenniums, the number of babies born in each thus becoming available for comparison with the number of babies born in respective quinquenniums in the general population. This afforded an unexpectedly striking picture, as seen in the accompanying table:

Role of Advancing Maternal Age in Causing Mongolism; a Comparison of Births of Mongoloid Imbeciles Occurring in Nine Quinquenniums with Births Occurring in the General Population of the United States in Similar Periods

2,095,939 Births in United States in 1934*			2,822 Births of Mongoloid Imbeciles	
Number of Births	Percentage	Quinquenniums	Percentage	Number of Births
261,345	12.4	(1) 15-19 yr.	3.4	98
637,480	30.4	(2) 20-24 yr.	10.8	306
544,068	25.0	(3) 25-29 yr.	14.0	396
353,949	16.8	(4) 30-34 yr.	16.9	478
106,811	0.9	(5) 35-39 yr.	23.8	674
73,385	0.3	(6) 40-44 yr.	23.6	668
7,090	0.03	(7) 45-49 yr.	3.8	108
110	0.005	(8) 50-54 yr.	0.2	6
		(9) 55-59 yr.	0.1	4

* Babies in the general population born to women under 15 years of age are not included.

In the first quinquennium, that of mothers from 15 to 19 years old, occurred 12.4 per cent of all births in the general population; the figure for the births of mongoloid imbeciles was 3.4 per cent, or one-fourth

the number to be expected. On study of the entire table it is seen that this is the low point for the occurrence of mongolism in relation to maternal age and therefore the period of the lowest risk for child bearing, so far as mongolism is concerned, the rule being that the younger the mother the less the likelihood of a child afflicted with mongolism. This will be discussed again in considering factor 3 of this study.

In the second quinquennium, that including the ages from 20 to 24 years, when fecundity, at least in this country is at its height, with 30.4 per cent of all births occurring in this period, the incidence of mongolism is represented by 10.8 per cent, or about one third of the normal expectancy. This is higher than one fourth but still far below normal expectancy, and therefore this period also is relatively safe, although less safe than the first quinquennium. In the third five year period the incidence of births of normal children[10] drops to 25 per cent and that of children with mongolism rises to 14 per cent, or slightly more than half, indicating that the risk has about doubled when the maternal age of 25 to 29 is compared with that of 15 to 19.

In the fourth quinquennium, i. e., when the mothers are 30 to 34 years old, the expectancy of mongoloid imbeciles equals the expectancy of normal children; and the relative security of the early years of womanhood as to mongolism has passed.

In the fifth quinquennium, that of ages from 35 to 39 years, when the decline from the optimum period of child bearing has become pronounced, the mothers producing but 0.9 per cent of the births in the general population, the incidence of births of mongoloid imbeciles rises to 23.8 per cent, a ratio of 25:1, and what might be called the mongolism zone has been reached. This, however, is not the period of greatest risk, since the rise continues after it: Mothers in the sixth five year period, i. e., mothers of 40 to 44, surpass threefold mothers of the preceding period in the probability of offspring with mongolism, the figures having changed to 0.3 per cent for the normal children and 23.6 per cent for those with mongolism, which is a ratio of about 75:1. In the seventh period this ratio rises to about 125:1, and in the eighth period it is about 40:1, the figures being 0.2 per cent for the infants with mongolism and 0.005 per cent for the normal infants. The last, or ninth, period cannot be compared because it is only the mothers of children with mongolism who are producing at all, the mothers in the general population having reached the end of the reproductive period at the age of 54. This point is further discussed in the consideration of factor 8.

10. The term normal is, of course, used for convenience only: it applies to the average child born in the general population.

It was thus not possible to detect at what point maternal aging begins to operate in the production of mongolism, nor do we believe that any such point exists. On the contrary, it is seen from these figures that although mongolism may occur in a child born of a mother at any age, women pass through a period of relative safety until the optimum period of child bearing is passed, the risk of bearing offspring with mongolism increasing in direct proportion to advancing age throughout the period of fecundity, being least at the beginning and greatest at the end. The likelihood of mongolism increases in direct relation to the number of menstrual cycles through which a woman has passed. Rosanoff and Handy have drawn attention to this point.[11]

ADVANCED PATERNAL AGE

A chart relating to the age of the father would, of course, show much the same picture as is here presented for maternal age. This is generally considered to be purely coincidental. Armstrong [12] said that "there is no evidence known to me that the children of elderly men tend to mongolism otherwise than when their wives are approaching the menopause." Jenkins [8] said that "the increasing incidence of mongolism with the increasing age of the father is totally explainable as a result of the correlation between the ages of the parents." Penrose,[4a] from a mathematical study of 150 cases, concluded that "paternal age is not a significant factor, while maternal age is to be regarded as very important," and after successfully disentangling the paternal from the maternal role he added: "paternal age need not be considered a significant causal factor." Lastly, Rosanoff and Handy [11] stated that "the age of the father apparently has no direct bearing on the etiology" of mongolism.

These may be accepted as authoritative opinions on this point, and the role of advanced paternal age in the production of mongolism may be discarded.

IMMATURITY OF THE MOTHER AND PRIMOGENITURE

The fate of a first-born child has been described as somewhat more uncertain than that of the other siblings. His height and weight, his intelligence quotient and his life expectancy are all less, and he shows

11. Rosanoff, Aaron J., and Handy, Leva M.: Etiology of Mongolism, Am. J. Dis. Child. **48**:764 (Oct.) 1934.

12. Armstrong, Hubert: Etiology of Mongolism with a Case of Mongol Twin, Brit. M. J. **1**:106 (June 30) 1928.

a higher incidence of disease, abnormalities and neuropathic tendencies.[13] Twenty-four per cent of a group of mentally defective children were found to be first born.[14] It is therefore of more than passing interest to inquire into the possible role of primogeniture in producing mongolism.

As for the role of the immature mother, Mackintosh [15] and Carson [16] stated that when a mongoloid imbecile appears in a first or second pregnancy the mother is usually young, and this has been a common conclusion to which many have subscribed.

Somewhat to my surprise, neither of these factors was apparent in the present study, in which among 2,947 women producing children with mongolism only 479, or 18 per cent, were primiparas, which is a low minority, decidedly too low to carry any weight. Moreover, the average age of these primiparas was 27.1 years, three years more than the peak maternal age for all women, as was seen in chart 1, and is, of course, out of line. When primiparas are above the average maternal age in such large groups as these, something is radically wrong, and the explanation is unescapable that the mongoloid imbecile usually is born of an older mother, without regard to whether she is a primipara or a multipara. Thus, even the force of primiparity is not sufficient to neutralize the force of advanced maternal age in the production of mongolism.

But there is a still more illuminating item. In chart 2, the lighter line to the left shows the maternal age of primiparas in the United States in the year 1934 (exclusive of Massachusetts and New Hampshire). It was made from figures compiled for this study in the Bureau of the Census by the acting chief statistician, Dr. John Collinson. Of 689,832 primiparas, the peak age was 19, with 72,956 births, and the average was 22.5, which is nearly five years less than the average age of primiparas bearing children with mongolism. And instead of dropping off after the optimum period of child bearing has passed, the line for the children with mongolism holds up, 30 per cent of the births occurring after the primiparous mother had passed the age of 30 years, which may to great profit be compared with the figure of 6.4 per cent for the normal children born to primiparas after the age of 30.

Here again the advanced age of the mother dominates, and neither primogeniture nor immaturity of the mother is a determining factor.

---

13. (*a*) Thurstone, L. L., and Jenkins, R. L.: Order of Birth, Parent Age and Intelligence, Chicago, University of Chicago Press, 1931. (*b*) Pearson, Karl: On the Handicapping of the First Born, London, Dulau & Co., 1914; cited by Thurstone and Jenkins.[13a] (*c*) Still, G. F.: Place-in-the-Family as a Factor in Disease, Lancet **2**:795 (Oct. 15); 853 (Oct. 22) 1927.

14. Langdon-Down, G.: On Some of the Mental Affections of Childhood and Youth, London, J. A. Churchill, 1887.

15. Mackintosh, J. M.: The Etiology of Mongolism, Brit. M. J. **2**:129 (July 21) 1928.

16. Carson, J. C.: The Mongolian Type, J. Psycho-Asthenics **12**:44, 1907-1908.

A BROAD DIFFERENCE IN THE AGES OF THE PARENTS

It was pointed out in the discussion of factor 2 that all the evidence is on the maternal side. If this is acceptable, there would appear to be no good reason for inquiring into discrepancies which may exist in the ages of the parents. If without influence, the father is without influence regardless of his age or of how much younger or older he may be than the mother.

That this is true was shown by Penrose,[4a] who placed the ages of both parents opposite the pooled parental age of the general population and found that they tallied. Jenkins[3] analyzed this item and found that it was not a factor, and Wile and Orgel[7] came to the same conclusion.

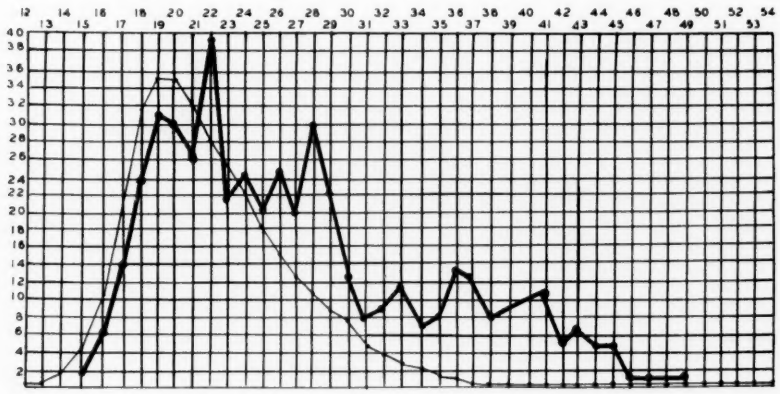

Chart 2.—Primiparity and maternal age in relation to mongolism; a study of 479 mongoloid imbeciles born to primiparas; the average age was 27.1 years. (Each horizontal line represents an afflicted child born to a primipara and 2,000 children born in the United States [exclusive of Massachusetts and New Hampshire] in 1934.)

This graph shows that primiparas bearing mongoloid imbeciles are almost 5 years older than primiparas in the general population. Of primiparas bearing mongoloid imbeciles, 30 per cent were more than 30 years of age. In this country, 6.4 per cent is the normal expectancy of primiparas more than 30 years of age.

LOW FECUNDITY AMONG WOMEN BEARING CHILDREN WITH MONGOLISM

It has been stated by a good authority (Jenkins[3]) that women bearing mongoloid imbeciles are of low fecundity. Because of the biologic possibilities attaching to such a statement this point was studied, and it was found that the 2,947 women of this group had produced 14,813 children—and how many more is unknown. This gave

an average of 5 children for each, which is comparable to the estimated fertility of the women of Russia and is almost twice that of French women.[17] It was also interesting to note that the woman bearing a mongoloid imbecile may remain fertile long after the average woman has stopped bearing children. Among the mothers of the 2,000,000 children born in the United States in 1934, the oldest was 54, whereas among the women of this special group some were still producing at 56, at 59 and even at 60 years of age (chart 3).

These data do not, therefore, support the suggestion that women bearing children with mongolism are of low fertility, nor do they indicate that any biologic importance may be attached to this theory.

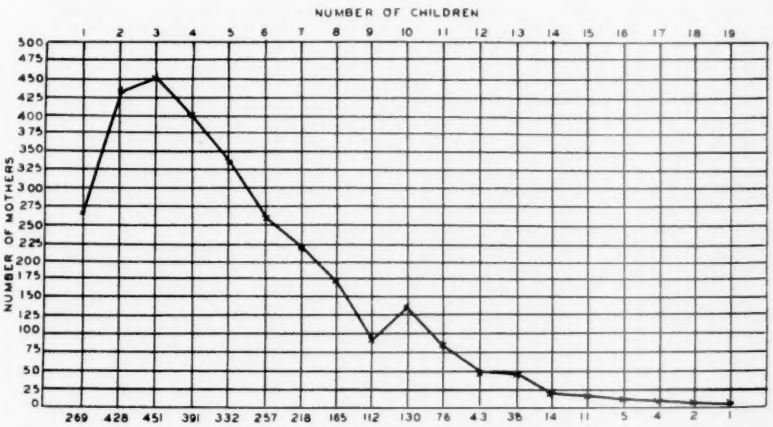

Chart 3.—The fertility of 2,947 women bearing children with mongolism. These women bore 14,813 children, an average of 5 each.

A PROLONGED INTERVAL PRECEDING THE BIRTH OF THE MONGOLOID IMBECILE

This factor, also known as that of the period of reduced fecundity, has received a considerable amount of attention by eminent students of this subject. It was mentioned by Langdon-Down in a discussion of a paper by Shuttleworth [2] published in 1909. Interest in the subject was greatly enlivened by Stekhoven's [18] contribution, which showed that the interval preceding the arrival of 91 mongoloid imbeciles was appreciably greater than that which preceded the births of 1,570 normal children, the mothers of both groups being past the age of 40. Van der

17. Newsholme., Arthur: The Elements of Vital Statistics, New York, D. Appleton & Company, 1924.

18. Stekhoven, W. S., cited by Jenkins.[3]

Sheer [19] expressed a similar belief. Still [13c] confirmed these conclusions and even ventured the suggestion that the risk of begetting a child afflicted with mongolism or otherwise defective may be proportionate to the interval since the birth of the last baby, six years between pregnancies being considered long and twelve dangerous. Further support was contributed by Jenkins,[3] who found that "the birth of a mongolian idiot is much more frequently preceded by a long gap than is the birth of a normal child, even when maternal age is controlled."

This is quite an array of authority in favor of the theory that the long gap between pregnancies is a factor in producing mongolism, and one would be strongly disposed to accept such opinions were they not at variance with those of Penrose, who has repeatedly distinguished himself through his mathematical studies of the moot factors in this particular phase of the etiology of mongolism. In a study of 224 cases among 1,031 pregnancies, Penrose [4b] concluded that "there is no evidence that the long interval which sometimes precedes the birth of an affected child is of causal significance." He also pointed out that the long interval more often follows than precedes the appearance of the child with mongolism.

It seems best, therefore, to await more complete data on this factor. We venture the suspicion that as time goes on the opinion of Penrose will be sustained.

REPRODUCTIVE EXHAUSTION FROM A LONG LINE OF PREGNANCIES, AS REVEALED BY STUDY OF THE BIRTH ORDER

That a mongoloid imbecile often appears at or near the end of a long line of pregnancies is well known. That this is due to reproductive exhaustion is not known; it has often been assumed.

Early in the study of mongolism, Shuttleworth [2] (1909) said that reproductive exhaustion might be a potent factor and was associated in some way with advanced maternal age. This is still commonly heard. Chart 4 represents the birth position of children with mongolism from the first to the nineteenth pregnancy in 2,897 cases. If one starts with their appearance in the nineteenth and works backward to the first pregnancy, one finds the nineteenth pregnancy represented by 1 mongoloid imbecile, the eighteenth by 1, and the seventeenth by 2. Eight mongoloid imbeciles were born in a fifteenth pregnancy, 29 in a twelfth, 99 in a tenth, 140 in an eighth, 184 in a seventh, 287 in a fifth,

19. van der Sheer, W. M.: Beiträge zur Kenntnis der Mongoloiden Missbildung, in Bonhoeffer, K.: Abhandlungen aus dem Neurologie, Psychiatrie, Psychologie und ihren Grenzgebieten, Berlin, S. Karger, 1927, vol. 41, pp. 1-162.

344 in a fourth, 398 in a third, 498 in a second and 518 in a first. Thus the highest number of births of mongoloid imbeciles occurred in first pregnancies, when reproductive exhaustion did not exist.[20]

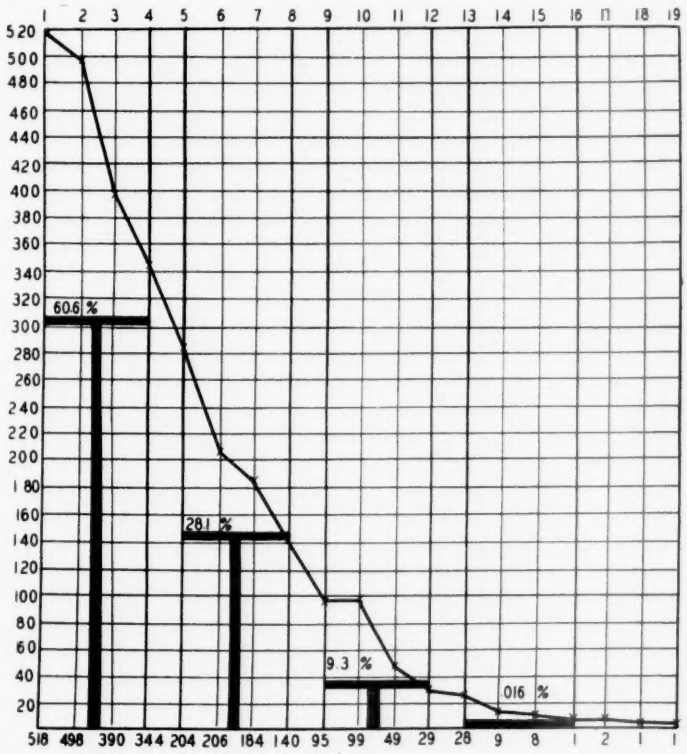

Chart 4.—The birth position of 2,897 mongoloid imbeciles. The highest number of births of mongoloid imbeciles occurs in the first pregnancy; in all succeeding pregnancies the number declines. As reproductive powers wane, the proportion of such births falls; it does not rise.

---

20. I am aware that the assertion that the highest number of births of mongoloid imbeciles occurs in a first pregnancy will be somewhat startling to many students of mongolism and to those especially who have come to believe that maternal age plays a role, and indeed it was to me. It is the first time that such a statement has been made in the literature, and it will not go unchallenged. There can, however, be little doubt that it is correct, for the following reasons: 1. The group is large enough for reasonable safety in reaching such a conclusion (2,822 cases). 2. The cases were derived from most parts of this country and are therefore not influenced by the social conditions of particular communities. 3. The rise from the last to the first is so consistent as to make such expectancy probable. The original data as received from the various institutions are available for study.

The next highest number of mongoloid imbeciles came in the second birth position, that is, preceded by only one pregnancy; the third highest number came in the third pregnancy and the next highest in the fourth. The number does not rise with the supposed wearing out of reproductive powers; it falls! These first four pregnancies provided slightly more than 60 per cent of all the births of children with mongolism, at too early a time to be related to reproductive exhaustion.

One may compare this proportion, 60 per cent, with the proportion appearing in the next four pregnancies, 28 per cent, less than one-half the number in the first four. Then in the succeeding four pregnancies, the ninth, tenth, eleventh and twelfth, when exhaustion might well come into play, the figure drops again, markedly; in the next 4, as the end of fecundity is approached, the base line is reached, the curve falling consistently all the way from the first pregnancy to the last.

In chart 1 a close relation between mongolism and advanced maternal age was seen, and in chart 2 it was noted that primiparas bearing children with mongolism were older than primiparas bearing normal children. Therefore, both reproductive exhaustion and primiparity fail to show their influence in mongolism when set squarely against advanced maternal age, which prompts the conclusion that neither of them is of etiologic importance.

It may be said that this is not a fair conclusion, as all women who have babies must have at least 1 child and more women have 1 than 2, more 2 than 3, and so on, so that the expectancy of birth of a child with mongolism must diminish directly as the total number in each birth position diminishes. This situation has also been delved into by the mathematical genius of Penrose,[4c] who showed that the number of mongoloid imbeciles in each birth rank closely approximates the number expected on the assumption that mongolism depends on maternal age and not on birth rank. "Aetiological significance," he stated, "cannot be attributed to birth order with any reasonable degree of probability." In a second paper on this subject he concluded: "If birth rank has any influence on the incidence of mongolism, it is too slight to be detected." Thus he placed full weight on maternal age alone.

ULTIMOGENITURE

Lind [21] has stated that were a mongoloid imbecile born to his wife he would see to it that there were no other children. This statement may throw some light on the fact that 200 of the mongoloid imbeciles in this series who were the first born were also the last born, and it suggests that many unfortunate parents of mongoloid imbeciles may

21. Lind, W. A. T.: Mongolian Idiocy, M. J. Australia **2**:272 (Sept. 15) 1923.

have been guided by a similar decision. Contraception must therefore be given its place in a study of the apparent significance of the last-born child afflicted with mongolism.

There were 1,942 supposedly complete families in this series, and the child with mongolism was the last born in 1,108. This is 57.1 per cent, leaving 43 per cent, or almost half, the families in which normal children appeared after the birth of the afflicted child; in some instances there were 8, 9 or even 10 later children. Were all these families complete, which I have good reason to think they were not, the figure would be still higher and the place of the child with mongolism as the last born still lower. A glance at such data makes the significance, if there is any, of ultimogeniture decidedly unimpressive.

PATERNAL REPRODUCTIVE EXHAUSTION

It was pointed out in the discussion of items 2 and 5 that all evidence at this time is against a paternal role in the production of mongolism. It is felt that this adequately disposes of paternal reproductive exhaustion as a factor.

CONCLUSIONS

My conclusions coincide with those of Jenkins and Penrose; I find that the role of advanced maternal age in causing mongolism is undeniable.

The peak maternal age in the general population in this country in the year 1934 was 24; the peak age of the mothers producing mongoloid imbeciles in this series of 2,822 cases was 41.

The incidence of mongolism increases steadily through the childbearing period, being lowest at the beginning and highest at the end, the likelihood of producing a mongoloid imbecile increasing in direct proportion to the number of menstrual cycles through which a woman has passed.

By comparing the number of mongoloid imbeciles born in each quinquennium of maternal age with the number of children born to mothers of similar age groups in the general population, it was found that the risk of bearing offspring with mongolism in the first quinquennium, 15 to 19 years, is only one-fourth the expectancy of births of normal children, this being the period of greatest safety so far as mongolism is concerned. In the second five year period (20 to 24 years) the expectancy rises to one-third; although a period of relative security, it is less secure than the first. In the third quinquennium (25 to 29 years) the expectancy of births of afflicted children rises to one-half that of births of normal children, and in the fourth (30 to 34 years) the number of children with mongolism and the number of normal children become equal; the protection of early womanhood against this type

of imbecility in her offspring has passed. In the succeeding quinquennium (35 to 39 years), as normal fecundity declines, the percentage of births of children with mongolism as compared with the percentage of births of normal children rises prodigiously, to 25 : 1, showing a definite predisposition to mongolism; what may be not inappropriately called the mongolism zone of maternity has been entered. The succeeding five year period (40 to 44 years) shows a further increase to 75 : 1, the seventh period going on up to 125 : 1.

Satisfactory evidence could not be found of the competence in relation to the etiology of mongolism of the following factors: advanced paternal age; immaturity of either parent; primogeniture; ultimogeniture; birth rank; the broad difference in the ages of the parents; the prolonged interval preceding the birth of the child with mongolism; low fertility, and reproductive exhaustion of either parent.

It is probable that the apparent relation of any of these factors to mongolism can be explained through the admixture of advanced maternal age.

819 University Club Building.

HYPERTROPHY OF THE HEART IN INFANTS

H. EDWARD MacMAHON, M.D.

BOSTON

The literature dealing with cardiac hypertrophy in infancy has increased year by year since the early papers of Simmonds [1] and Oberndorfer,[2] which appeared in 1899 and 1906, respectively. No longer may the term "congenital idiopathic hypertrophy" be applied to every enlarged heart in infancy—excluding, of course, those showing gross morphologic anomalies in development. A careful study of individual cases has shown a varied etiology, including coarctation of the aorta, renal insufficiency, primary or essential hypertension, disturbed carbohydrate metabolism accompanied with the storage of excess glycogen in the fibers of the muscle and diffuse myocardial fibrosis secondary to myocardial injury. In a comparatively small number of cases, however, the use of the term "congenital idiopathic hypertrophy" is still warranted, for they present a definite clinical and pathologic entity, the source of which still remains obscure. Abbott [3] described this entity as being "characterized by great cardiac enlargement in the absence of myocardial disease or other extra and intra cardiac etiological factors, a pure or primary hypertrophy of the muscle fibres alone existing." Steiner and Bogin [4] have recently pointed out that this form of primary cardiac enlargement may at times be associated with the condition of status thymicolymphaticus.

When the problem of cardiac hypertrophy in infants is approached from the standpoint of morphogenesis, it appears that three separate histologic changes may account for this increase in the weight of the heart. First, there is a group of cases in which the increase in weight of the heart has been explained mathematically by a corresponding and carefully measured real hypertrophy of the individual fibers of the

---

From Tufts College Medical School.

1. Simmonds, M.: Ueber congenitale primäre Herzhypertrophie, München. med. Wchnschr. **46**:108, 1899.

2. Oberndorfer: Herzhypertrophien im frühesten, Verhandl. d. Versamml. d. Gesellsch. f. Kinderh. **23**:181, 1906.

3. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, The American Heart Association, 1936.

4. Steiner, M., and Bogin, M.: Idiopathic Cardiac Enlargement Associated with Status Thymicolymphaticus, Am. J. Dis. Child. **39**:1255 (June) 1930.

cardiac muscle. In a second group, an excessive deposition of glycogen has led to extreme swelling of the muscle fibers—a pseudohypertrophy. The third group comprises cases in which an increase of connective tissue, appearing as a diffuse myocardial fibrosis, has been the most striking histologic change.

A reasonably careful survey of the literature bearing on this subject has revealed no mention of myocardial hyperplasia as a possible factor in the histogenesis of cardiac hypertrophy in infancy.

A careful histologic examination of the myocardiums of infants whose hearts were definitely increased in weight, comprising infants with primary idiopathic hypertrophy as well as some with hypertrophy of the left ventricle of renal origin and some in whom the condition was secondary to coarctation of the aorta, has revealed not one but many mitotic figures in varying phases of nuclear division. No part of the myocardium has been exclusively favored, although the figures appear most numerous in the outer portions of the myocardium and toward the tip of the left ventricle. Mitoses have been found in the fibers of the cardiac muscle in cases of cardiac hypertrophy in children up to 20 months of age. It is possible that this should be considered not as an example of true hyperplasia but merely as an acceleration of a normal physiologic process, in which the child's heart at this stage is still undergoing natural histogenesis. The interpretation, however, seems of secondary importance, for the fact remains that during the first and second years a proliferation of myocardial elements can and does occur in infants with cardiac hypertrophy. The extreme rarity of mitoses in the fibers of the cardiac muscle in average-sized hearts of infants, even during the first and second months of life, has led investigators to believe that the active proliferation of nuclei in the cardiac muscle under ordinary conditions ceases early.

A study of this problem was prompted by the chance observation of an unusually large number of mitoses in the myocardial fibers of the greatly enlarged heart of a 6 month old child. The child died in uremia resulting from an anomalous development of both ureters, which caused intermittent obstruction of the urinary tract. The heart of this child was well formed and showed no developmental anomalies. It weighed 60 Gm., which is just twice the average weight for the heart of a child of the same age and size. The left ventricle was large, and the ventricular wall was uniformly thickened. Nuclei in various stages of mitotic division were found (figs. 1 and 2), and in some low power fields as many as three or four mitoses were seen (fig. 3). In addition to this multiplication of nuclei, the growth of the muscular fibers and the formation of myofibrils were clearly recognizable. Many of the fibers showed true hypertrophy as well.

Abbott in her recently published monograph gave an excellent review of the hypertrophies of hearts in children. She made no mention, however, of the rôle proliferation of muscular elements may play in the histogenesis of this interesting condition, but she did refer to a case, originally reported by Sprague, Bland and White,[5] of "congenital so-called idiopathic hypertrophy" which later proved by microscopic examination to be the seat of von Gierke's disease (cardiomegalia glycogenica). The heart weighed 175 Gm., five times its normal weight (34 Gm.). It pre-

Fig. 1.—Section of myocardium (× 900) showing a mitotic figure in a fiber of the cardiac muscle. A complete spindle with centrosomes is visible. The chromatin is arranged at the center of the spindle, forming a rather uneven equatorial plate. The chromatin is in the form of coarse granules and rods. The cytoplasm at the site of nuclear division is comparatively clear and finely granular. Above and below the nucleus the cytoplasm becomes gradually denser; it stains more deeply, and fine transverse striations appear before individual myofibrils are recognizable. The adjacent fibers show normal branching. There is moderate hypertrophy of the individual fibers, with an increase in the number of myofibrils in each fiber.

sented a large globular contour. Microscopic examination showed the fibers to be only twice their normal size. This strongly suggested that

5. Sprague, H. B.; Bland, E. F., and White, P. D.: Congenital Idiopathic Hypertrophy of the Heart, Am. J. Dis. Child. **41**:877 (April) 1931.

a moderate hyperplasia might have been present as well. This type of enlargement has also been stressed by Bischoff,[6] Putschar,[7] Pompe,[8] Humphreys and Kato [9] and, most recently, Ellis.[10] Each of these investigators spoke of the extraordinary vacuolation of the muscle fibers, accompanied with the deposition of large quantities of glycogen, especially about the nucleus, but none mentioned the possibility of hyperplasia occurring as well.

Levine [11] recently described a case of cardiac hypertrophy associated with coarctation of the aorta occurring in a 10 month old child. The heart was greatly enlarged and weighed 150 Gm., which is several times the normal weight for that age. The left ventricle showed not only hypertrophy of the myocardium but a uniform and diffuse thickening of the endocardium as well. The histologic observations were of special interest, for neither the individual fibers nor their nuclei appeared to be increased in size. Nothing was said of the possibility of hyperplasia, but so large a heart accompanied with no change in the size of the muscle fibers would lead one to conclude that hyperplasia of muscular elements had taken place.

Taussig and Remsen,[12] in reporting the finding of essential hypertension in a boy 2 years of age, pointed out the rarity of this condition in children and drew attention to the presence in their case of an enormously enlarged heart, weighing 220 Gm. On histologic examination the only changes recognizable in the heart were hypertrophy of the muscle fibers and slight scarring of the myocardium. This is one of the very few cases in which cardiac hypertrophy has been reported in infants in association with primary or essential hypertension. There was no associated chronic progressive renal disease, no congenital malformation of the kidneys or urinary tract, no infection of the urinary system, no coarctation of the aorta, no pituitary or adrenal tumor and, finally, no cerebral tumor that might explain the elevated blood pressure.

---

6. Bischoff, G.: Zum klinischen Bild der Glykogen—Speicherungskrankheit (Glykogenose), Ztschr. f. Kinderh. **52**:722, 1932.

7. Putschar, W.: Ueber angeborene Glykogenspeicherkrankheit des Herzens—"Thesaurismosis glycogenica" (v. Gierke), Beitr. z. path. Anat. u. z. allg. Path. **90**:222, 1932.

8. Pompe, J. C.: Hypertrophie idiopathique du coeur, Ann. d'anat. path. **10**:23, 1933.

9. Humphreys, E., and Kato, K.: Glycogen-Storage Disease, Am. J. Path. **10**:589, 1934.

10. Ellis, R. W. B.: Congenital Hypertrophy of Heart? (Cardiomegalia Glycogenica), Proc. Roy. Soc. Med. **28**:1330, 1935.

11. Levine, H. D.: Cardiac Hypertrophy in Infancy, Am. J. Dis. Child. **48**: 1072 (Nov.) 1934.

12. Taussig, H. B., and Remsen, D. B.: Essential Hypertension in Boy of Two Years of Age, Bull. Johns Hopkins Hosp. **57**:183, 1935.

In addition to these two groups, one in which the storage of glycogen and the other in which true hypertrophy of muscle fibers has been considered the basis for increase in size of the heart, there is a third, rather heterogeneous, group, described originally by Stoloff [13] and characterized by the presence of a diffuse increase in connective tissue throughout the myocardium. The first case reported by Stoloff appeared in a 15 month old infant. The heart weighed 155 Gm. and showed an enlargement of both ventricles. Histologically, in addition to the fibrosis, hypertrophy of muscle fibers was occasionally seen. Kugel and Stoloff [14] a few years

Fig. 2.—Section of myocardium (× 900) showing mitotic nuclear division in a fiber of the cardiac muscle, with growth of the fiber and development of myofibrils. The entire spindle is recognizable, including one centrosome. The chromatin, appearing as clumps of granules and short rods, is gathered in the center of the spindle to form an equatorial plate. There is a clear zone about the spindle. Myofibrils showing transverse striations are seen at each side of the nucleus; above and below the nucleus the chromatin is more deeply stained, and transverse striations are visible in the myoplasm before the longitudinal myofibrils are clearly seen.

---

13. Stoloff, E. G.: So-Called Idiopathic Enlargement of the Heart in Infancy and in Childhood, Am. J. Dis. Child. **36**:1204 (Dec.) 1928.

14. Kugel, M. A., and Stoloff, E. G.: Dilatation and Hypertrophy of the Heart in Infants and in Young Children, Am. J. Dis. Child. **45**:828 (April) 1933.

later reviewed this lesion and stated that there was a reparative process in the form of a replacement fibrosis and degeneration and atrophy of the cardiac musculature. However, if atrophy and disappearance of muscle fibers take place in this group of cardiac hypertrophies, a group in which the heart may grow to several times its normal weight, there must be an overwhelming excess of connective tissue throughout the myocardium. The result would be a reversal of the ratio of the parenchymatous tissue to the mesenchyme, unless a regenerative proliferation of muscular elements compensated for those that disappeared.

Fig. 3.—Section of myocardium (× 400) showing four mitotic figures in the fibers of the cardiac muscle. In three of these the chromatin is rather scattered, whereas in the fourth it forms a central, or equatorial, plate in a recognizable spindle (monaster). In each the cytoplasm surrounding the dividing nucleus is relatively clear, and longitudinal fibers appear only at the margins of the cells. The capillaries are dilated; the stroma is edematous. There is evidence of myocardial hyperplasia, congestion and edema.

SUMMARY

A review of the types of cardiac hypertrophy in infants clearly shows that many different factors may play important etiologic rôles. Furthermore, when considered from a structural standpoint, the histologic picture is likewise variable. One change has been almost universally

emphasized, namely, an increase in the size of the individual muscle fibers, whether in true hypertrophy or in a mere pseudohypertrophy resulting from the storage of glycogen. The purpose of this brief report is to point out that in cardiac hypertrophy appearing at an early age, in addition to the increase in size of the muscle fibers, there may be a true proliferation of these elements. A corollary to this is the suggestion that since proliferation of the fibers of the cardiac muscle may occur in hypertrophies of this group, it is possible that during the same period myocardial regeneration following severe injury may likewise occur.

GONADOTROPIC PRINCIPLE IN THE TREATMENT OF CRYPTORCHIDISM

A REVIEW OF THE LITERATURE

J. A. BIGLER, M.D.
HIGHLAND PARK, ILL.

L. M. HARDY, M.D.
CHICAGO
AND
H. V. SCOTT, M.D.
FORT WAYNE, IND.

Within the past one hundred years the problem of cryptorchidism has occupied the minds of many members of the medical profession. Originally the patient consulted his physician in the hope of improving the anatomic condition so as to be the equal of his fellowmen. Since that day, however, many new problems have arisen, concerned mainly with the desire for complete fertility and the insurance against possible malignant changes in the ectopic organ.

In 1820 Koch, of Munich, performed the first orchidopexy. Unfortunately this operation was unsuccessful, as was the second operation, performed by Chelins. Sixty years later the first surgical cure was reported by Wood, and since that time there has been a growing interest in the surgical treatment of cryptorchidism. Numerous methods of procedure have been offered; some forms of technic have been entirely original, while others have been modifications of methods previously described. Many surgeons have been interested in this problem, and in the review of the literature one sees often the names of Max Schüller, Bevan, Torek, Keetley, Ombrédanne, Cabot, Burdick, Coley, Wangensteen, Walters, Theissen, McKenna and others. Some have been dissatisfied with the general results, particularly with the atrophy which may occur in the testicle postoperatively. From a study of the German literature up to 1922 it is seen that in 50 per cent of the cases the operation was reported as a failure. Since that time there have been numerous reports in this country of the records of operations in this field, and the percentage of cures has ranged from 42 to 92. Nevertheless, many physicians have held the hope that in

---

From the Children's Memorial Hospital.

Presented before the Chicago Pediatric Society, April 20, 1937, and before the American Pediatric Society, April 29, 1937.

this day of expanding knowledge about the glands of internal secretion a form of therapy could be found to assist in the treatment of the undescended testicle.

EMBRYOLOGY

Until the fourth week of embryonal life the gonads are undifferentiated organs derived as mesothelial thickenings of the anteromedian surface of the wolffian bodies (mesonephron). This mass grows, becomes the germinal ridge and contains differentiated epithelial cells embedded in its connective tissue. By the fifth week the wolffian and müllerian ducts are found longitudinally traversing the germinal ridge. In the sixth week of fetal life the genital ridge extends from the sixth to the twelfth dorsal segment, lying on the inner side of the wolffian ridge.[1] By the third month, owing to atrophy of the cranial segments, each testis gradually assumes a position in the iliac fossa near the internal abdominal ring. At this point a process of peritoneum, known as the processus vaginalis, precedes further descent and extends through the internal ring, inguinal canal and external ring and into the lower portion of the scrotum. The testis then passes through the abdominal wall by way of the inguinal canal to the external abdominal ring at approximately the seventh or the eighth month. At the time of birth the upper end of the vaginal process gradually becomes obliterated, and the lower portion, the tunica vaginalis propria, remains open. Failure of the upper part to fuse results in potential hernia, thereby accounting for the hernia said to be associated in 85 per cent of cases of ectopic testis.[2] The gubernaculum is thought by some to contribute to the descent of the testicle. It is partly muscular and is attached to the epididymis; its principal fibers extend into the scrotum. The gubernaculum atrophies after descent, and in cases of ectopic testis it is often absent. Eisendrath and Rolnick [3] revived Lockwood's idea and described the gubernaculum as a fibro-elastic structure with four tails, terminating, respectively: (1) in the lower portion of the scrotum, (2) at the pubic bone, (3) in the tissue over Scarpa's triangle and (4) in the perineum. This may serve as an explanation of the fact that an ectopic organ is occasionally found in these areas. The exact mechanism of testicular descent is unknown, and the theory that shortening of the gubernaculum actively draws the testicle down is no longer generally accepted. Engle [4] has stated that testicular descent is dependent on three factors: (1) the gubernaculum, which serves as a tract but is

1. Campbell, M. F., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 3, chap. 30.

2. Counsellor, V. S.: J. Urol. **30**:327, 1933.

3. Eisendrath, D. N., and Rolnick, H. C.: Textbook of Urology, Philadelphia, J. B. Lippincott Company, 1928, p. 402.

4. Engle, E. T.: Endocrinology **16**:506, 1932.

not affected by hormonal stimulation because it consists of unspecialized tissue, (2) a mechanical factor assisted by the various muscles and fascia and (3) the hormonal influence. It is interesting to note that Arey [5] did not mention the hormonal influence on testicular descent in his recent textbook.

INCIDENCE

It is universally agreed that ectopic testes are more frequently noted in children than in adults. In a series of 450 new-born boys, 10 per cent had undescended testicles, whereas in a similar series of premature boys there was an incidence of 32 per cent. Drake found 27 undescended testicles while examining 528 boys ranging in age from 9 to 20 years. Physical examinations recorded in the Austrian army revealed cryptorchidism to be present in 2.2 of each 1,000 men. Marshall found it in 11 of 10,800 men, and Rennie observed it in 6 of 10,000 soldiers. The Medical Department of the United States Army has reported it in 3.1 of each 1,000 recruits. A study of 18,140 children admitted to the Hospital for the Ruptured and Crippled, New York, revealed that in 3 per cent the condition was complicated with cryptorchidism. In another institution the records of 3,848 boys were studied, and an incidence of 2.2 per cent was found for boys between the ages of 14 and 21 years.

EARLY HISTORY AND ANIMAL EXPERIMENTATION

In 1839 John Hunter [6] stated that the undescended testis fails to reach the scrotum because of an inherent imperfection. Nearly one hundred years later Wangensteen [7] said that the ectopic testis owes its imperfection to its position. As early as 1902 Eccles [8] discussed the physiology of testicular descent and suggested a possible link with the glands of internal secretion. Cushing [9] and Aschner [10] carefully described their clinical findings in crptorchidism in 1910 and 1912.

Aschheim and Zondek [11] announced in 1926 that pituitary transplants induce precocious sexual maturity in immature rats. The same authors [12]

5. Arey, L. B.: Developmental Anatomy, Philadelphia, W. B. Saunders Company, 1934.

6. Hunter, J.: Animal Economy, London, Longman [and others], 1839, vol. 4.

7. Wangensteen, O. H.: Ann. Surg. **102**:875, 1935.

8. Eccles, W. M.: Lancet **1**:509, 1902.

9. Crowe, S. J.; Cushing, H., and Homans, J.: Bull. Johns Hopkins Hosp. **21**:129, 1910.

10. Aschner, B.: Arch. f. Gynäk. **97**:200, 1912.

11. Aschheim, S., and Zondek, B.: Ztschr. f. Geburtsh. u. Gynäk. **90**:372, 1926.

12. Aschheim, S., and Zondek, B.: Klin. Wchnschr. **6**:248 (Feb. 5) 1927.

reported that a gonad-activating hormone was present in the urine of pregnant women. Smith and Engle [13] quickly confirmed the work of Aschheim and Zondek and also compared the effects of transplanting substance from the anterior lobe of the pituitary gland into the muscles of rats, with gonadotropic principle given intramuscularly. There was a parallelism of results, but a much greater reaction was noted with the urinary extract. Engle [14] and Evans and Simpson [15] demonstrated clearly that the action of an extract from the urine of pregnant women was not identical with that of implants of hypophysial tissue. De Jongh,[16] using the gonadotropic principle from the urine of pregnant women, observed an increase in growth of secondary sexual characteristics in mice and rats and in normal or unilaterally castrated animals. No change was noted in spermatogenesis; all changes that did occur were confined to the interstitial tissues. Bourg [17] confirmed de Jongh's work and performed some interesting experiments on irradiated testes, realizing that irradiation is known to affect the interstitial tissues. Extract of the urine of pregnant women was then given and was followed by a development in the secondary sexual characteristics. Molien [18] expressed the belief that this principle only increases the output of androgen by the testis and secondarily causes sexual development. Balawenetz,[19] Kraus [20] and Butcher [21] worked with a variety of animals and found spermatogenesis to be affected by the extract of the urine of pregnant women. It is interesting to note that the primates are the only species in which the testes normally descend before or just after birth. In guinea-pigs, rats, squirrels and rabbits descent occurs either at puberty or during the breeding period.[22] Nelson [23] has reported that the gonads influence the functional activity of the hypophysis and has observed that as the testes of rats which were rendered cryptorchid underwent retrogressive changes, the hypophysis of these animals exhibited changes similar to those observed after castration. The injection of the gonadotropic factor into these animals

13. Smith, P. E., and Engle, E. T.: Am. J. Anat. **40**:159, 1927.

14. Engle, E. T.: Ovarian Responses: Differences Elicited by Treatment with Urine from Pregnant Women and by Freshly Implanted Anterior Lobe, J. A. M. A. **93**:276 (July 27) 1929; Endocrinology **16**:405, 1932.

15. Evans, H. M., and Simpson, M. E.: Am. J. Physiol. **89**:381, 1929.

16. de Jongh, S. E.: Arch. néerl. de physiol. **15**:470, 1930.

17. Bourg, R.: Compt. rend. Soc. de biol. **104**:1046 (July 18) 1930.

18. Molien, M.; D'Amour, F., and Gustavson, R. G.: Endocrinology **17**:295, 1933.

19. Balawenetz, S.: Virchows Arch. f. path. Anat. **278**:383, 1930.

20. Kraus, E. J.: Klin. Wchnschr. **9**:1493 (Aug. 9) 1930.

21. Butcher, E. O.: Anat. Rec. (supp.) **54**:49, 1932.

22. Huberman, J., and Israeloff, H. H.: J. Pediat. **7**:759, 1935.

23. Nelson, W. O.: Proc. Soc. Exper. Biol. & Med. **32**:1605, 1935.

resulted in the stimulation and restoration of the seminal vesicles and prostate, while the castration cells [24] disappeared from the hypophysis. So far no change has been found in the epithelium of the seminiferous tubules, but a marked stimulation has been observed in the interstitial tissue of the testes.[25] Castrated rats treated with the gonadotropic factor extracted from the urine of pregnant women showed no change in the sexual accessories or the hypophysis. Nelson [26] said he believed that the basophilic cells are responsible for the gonadotropic factor and that the suppressing influence of the gonads on the gonadotropic activity of the hypophysis is conducted through the action of the gonadotropic factor on the secretory cycle of the basophilic cells of the anterior lobe of the pituitary body. Therefore, the gonads are dependent on the hormones of the anterior lobe of the pituitary body for normal gametogenic and endocrine activities. Probably two or more hormones are produced by the testis, since the one best known does not give complete results in replacement after gonadectomy. This has been shown by the growth of the comb in the capon.

CLINICAL PROGRESS

Shortly after Aschheim and Zondek observed that a gonad-activating hormone was present in the urine of pregnant women, Schapiro [27] used an extract prepared from such urine (known as praehormone), proved its efficiency in human beings and reported that a large percentage of boys with cryptorchidism showed increased genital growth and testicular descent after this form of therapy. The extracts used clinically are similar in action but are known by various names. In this country the extracts used possess a potency of from 100 to 250 rat units per cubic centimeter. Injections have been given subcutaneously and intramuscularly with equal effects. In the majority of patients successfully treated, the dose varied from 1 to 3 cc., given one to five times weekly. The patients who reacted favorably required from 1,000 to 4,500 rat units.

At present there are eighteen reports in the literature, each dealing with a series of cryptorchid boys treated with the gonadotropic principle from the urine of pregnant women. Of the 191 patients reported on, 101 (or 52.8 per cent) possessed an endocrine type of obesity, and 90 (or 47.2 per cent) had a normal build. In all the patients there were

24. Smith, P. E., and Leonard, S. L.: Anat. Rec. **58**:145 (Jan. 25) 1934; Proc. Soc. Exper. Biol. & Med. **30**:1246, 1933.

25. Moore, C. R., and Price, D.: Am. J. Physiol. **99**:197, 1931. Riddle, O., and Polhemus, I.: ibid. **98**:121, 1931. Bourg.[17]

26. Nelson, W. O.: Endocrinology **19**:187, 1935.

27. Schapiro, B.: Deutsche med. Wchnschr. **56**:1605 (Sept. 19) 1930.

267 undescended testicles, 167 (or 62.5 per cent) of which showed complete scrotal descent after treatment. The detailed results are to be found in the accompanying table.

Many observers have encountered difficulties in examining for the ectopic testis and have felt that it is extremely important to examine the patient while standing as well as when prone. Invagination of the scrotum does not always reveal the ectopic testis, but if that method is combined with a gentle rolling motion of the finger-tips over the area of the canal a testicle the size of a pea may be found. Some of the observers have questioned the results of treatment, especially when descent occurred after the first or the second injection. It is desirable to keep in mind that an active cremasteric reflex may elevate the testicle high in the canal. Testicles which are migratory and capable of being reduced into the scrotum should be carefully observed before any treatment is started.

It is particularly interesting to study the reports of the patients with obvious endocrine disturbances. Dorff [28] in his excellent observations of 14 obese boys noted two distinct types. The obesity due to adiposogenital dystrophy was thought to be due to primary hypogonadism. In these boys there were signs of adiposity, general hypoplasia, eunuchoid proportions and normal osseous development, evidenced by the appearance of the carpal centers and the epiphysial nuclei. The second type was due to masked hypothyroidism, with retarded osseous development and hypoplastic testes, in addition to other symptoms of thyroid deficiency. The author concluded that: (1) the hypoplastic testes increase in size, (2) the undescended testes increase in size and descend to a lower point, (3) the genitalia enlarge and (4) a more rapid response to treatment is noted near puberty. Goldman and Stern [29] have reported a change in body measurements to a more masculine type in 5 of 7 patients with adiposogenital dystrophy. Allen [30] and Rubenstein [31] have reported on patients with diabetes insipidus coincident with bilateral cryptorchidism in whom there was testicular descent after therapy, besides a marked improvement in the general condition.

It is apparent that cryptorchidism of endocrine origin, whether it stands in a causal or a secondary relationship to pituitary dysfunction,

28. Dorff, G. B.: Maldevelopment and Maldescent of Testes: Report of Treatment with Anterior Pituitary-Like Gonadotropic Hormone from Urine of Pregnant Women, Am. J. Dis. Child. **50**:649 (Sept.) 1935.

29. Goldman, A., and Stern, A.: New York State J. Med. **33**:1095 (Sept. 15) 1933.

30. Allen, A. A., and Stokes, J. S.: Cure of Diabetes Insipidus Coincident with Bilateral Correction of Abdominal Cryptorchidism by Gonadotropic Factor from Pregnancy Urine, J. A. M. A. **106**:780 (March 7) 1936.

31. Rubenstein, H. S.: Endocrinology **18**:445, 1934; **20**:192, 1936.

Data on Undescended Testicles and Hormonal Treatment

Author	Number of Patients	Average Age, Years	Number of Undescended Testicles	Number of Obese Patients	Number of Patients with Normal Build	Preparation Used	Dosage	Results: Complete Descent of Testicle	Results: Percentage	Results: Partial Descent of Testicle	Genital Growth
Schapiro [27]	13	Over 11	14	11	2	Praehormone	3,000-4,000 R. U.	10	71	3	Yes
Aberle, S. B. D., and Jenkins, R.: J. A. M. A. **103**: 314, 1934	5	7	6	3	2	Extract of anterior lobe of hypophysis	1,700-4,500 R. U.	2	33	..	Yes
Cohn, S.: J. A. M. A. **103**: 103, 1934	6	9.5	8	2	4	Antuitrin-S	1,000-2,600 R. U.	6	75	1	Yes
Sexton, D. L.: Endocrinology **18**: 47, 1934	6	12.5	9	6	0	Antuitrin-S and follutein	300 R. U. daily	7	77	1	Yes
Kunstadter, R. H., and Robins, L. S.: J. Pediat. **4**: 774, 1934	3	10	5	3	0	Antuitrin-S	.....	5	100	..	Yes
Spence, A. W., and Scowen, E. F.: Lancet **2**: 1335, 1935	33	4-26	45	12	21	Extract of anterior lobe of hypophysis	500 R. U. twice weekly	29	64	..	Yes
Brosius, W. L.: Endocrinology **19**: 69, 1935	9	3-15	10	3	6	Antuitrin-S	3 cc. weekly	6	60	2	Yes
Dorff [28]	8	11	10	8	0	Follutein	8,000-45,000 R. U.	7	70	..	Yes
Webster, B.: J. A. M. A. **104**: 2157, 1935	12	11	15	5	7	Follutein	1,000-6,000 R. U.	13	86	1	Yes
Huberman and Israeloff [22]	5	11	8	0	5	Follutein	.....	3	37	3	Yes
Rubenstein [31]	9	10.5	10	9	0	Follutein	.....	9	90	1	Yes
Goldman and Stern [20]	11	13.5	11	7	4	Antuitrin-S	1,800-14,000 R. U.	10	90	..	Yes
Priestley, J. B., and Cohen, R.: J. Iowa M. Soc. **25**: 547, 1935	2	14	4	2	0	Extract of anterior lobe of hypophysis	.....	1	25	..	Yes
Sippe, C.: M. J. Australia **2**: 787, 1935	1	10	2	1	0	Extract of anterior lobe of hypophysis	.....	2	100	..	Yes
Hess, Kunstadter and Saphir [36]	13	5-14	26	5	8	Antuitrin-S	100-150 R. U. thrice weekly	19	73	..	Yes
Thompson and others [46]	18	1.5-17	21	6	12	Follutein	200 R. U. thrice weekly	4	19	..	Yes
Cramer, A. J.: Endocrinology **21**: 230, 1937	20	5-13	30	6	14	Antuitrin-S	500-1,000 R. U.	19	63	2	Yes
Werner, A. A.; Kelling, D.; Ellersieck, J., and Johns, G. A.: J. A. M. A. **106**: 1541, 1936	17	5-13	33	..	..	Gonadotropic extract of anterior lobe of hypophysis	10-20 R. U. 1 to 5 times weekly	24	73	..	Yes
Bigler and co-workers	23	2-13	31	3	20	Antuitrin-S	.....	14	45	7	Yes
	32	2-13	40	2	29	Gonadotropic extract of anterior lobe of hypophysis	.....	7	18	6	Yes
	16	2-13	20	1	15	Both extracts	.....	5	25	5	Yes

should be accompanied with evidence of this dysfunction. Katzman and Doisy[32] have shown that the urine of normal children contains little or no gonadotropic hormone. It is generally agreed that whenever gonadal function is diminished or absent, as in hypogonadism of adults,[33] the menopause,[34] or castration,[35] there is an excessive excretion of gonadotropic hormone, presumably of pituitary origin. Hess and his co-workers,[36] realizing that the clinical diagnosis of pituitary or other endocrine dyscrasia is subject to variable interpretation, have recently studied a group of cryptorchid patients, with particular interest in the urinary excretion of the gonadotropic hormone. Zondek's[37] alcohol precipitation method was used, and the authors concluded that the presence of the hormone in the urine of these patients justifies medical treatment and offers a good prognosis in the absence of mechanical obstruction. The absence of the hormone was said to be due to (1) functionally active testes and (2) primary pituitary dysfunction. For both conditions the authors said they believed that organotherapy should be tried and that in the event of failure surgical treatment is indicated. Perhaps this method of procedure will help in the selection of patients for medical treatment and will counteract the justifiable skepticism which has arisen owing to organotherapy in unselected cases.

SURGICAL ASPECT

For one hundred and seventeen years surgeons have been interested in the ectopic testis. Successful operative procedures have gradually been evolved, and today two methods are widely used. The Bevan operation is probably the better known. It consists chiefly of mobilizing the testicle and tying off the peritoneal attachments as in herniotomy. After elongation of the cord by dissection of the intervascular connective tissues, the organ is brought down and sutured to the lowermost part of the scrotum. Torek's method, which has rapidly gained approval, differs in that after the testis is brought into the scrotum the gland is sutured to the fascia of the upper inner portion of the thigh. This assures that the gland will stay in place; then from three to six months later the testis and scrotum are dissected from the thigh.

32. Katzman, P. A., and Doisy, E. A.: J. Biol. Chem. **106**:125, 1934.

33. Goldhammer, H., and Loewy, P.: Klin. Wchnschr. **14**:704 (May 18) 1935.

34. Evans, H. M.: Present Position of Our Knowledge of Anterior Pituitary Function, J. A. M. A. **101**:425 (Aug. 5) 1933.

35. Smith, P. E., and Engle, E. T.: J. Pediat. **5**:163, 1934.

36. Hess, J. H.; Kunstadter, R. H., and Saphir, W.: Urinary Excretion of Gonadotropic Hormone in Cryptorchidism, J. A. M. A. **108**:352 (Jan. 30) 1937.

37. Zondek, B.: Die Hormone des Ovariums und des Hypophysenvorderlappens, Berlin, Julius Springer, 1931.

Before the advent of organotherapy in cryptorchidism, many surgeons were treating this condition conservatively, mainly because the results were not completely satisfactory and atrophy of the testicle occasionally followed operation. It was observed by many that the vas deferens allows elongation, but the vascular supply to the testicle is conducted by exceedingly short vessels. Nevertheless the surgical procedure may be definitely indicated in view of the associated conditions, such as testicular pain, torsion of the spermatic cord, hernia, obstruction to descent, possible testicular neoplasm, decreased fertility and psychogenic disturbances.

Bevan [38] stated in 1929 that spontaneous descent does not occur after the age of 1 or 2 years unless the testicle can be manually forced into the scrotum. More recently Drake [39] has reported spontaneous descent of ten testicles before puberty, some of which could not be felt at first by the usual method of examination. Williams [40] has observed spontaneous descent in 87 per cent of 43 cryptorchid boys. Naturally, controversial ideas have arisen, and one is faced with such problems as: Does the ectopic testis during preadolescence always necessitate surgical intervention? Are etiologic factors amenable to surgical care? Harris [41] has recently placed the cryptorchid patients in two groups: first, those for whom no operative procedure is necessary, such as normal boys in whom descent will occur spontaneously, normal boys in whom hormonal therapy will produce descent and those patients with endocrine disturbances who seem to respond readily to organotherapy. His second group included those for whom surgical treatment offers the only hope for correction of the anatomic obstruction to descent.

At present there seem to be four methods of procedure in dealing with the undescended testicle: (1) watchful waiting, (2) surgical treatment, (3) hormonal therapy and (4) a combination of surgical treatment and organotherapy. Bevan has reported 42.5 per cent of surgical cures among 33 patients and recently suggested surgical treatment when organotherapy has been ineffectual over a period of six months. He also claimed that the surgical procedures are less difficult after preoperative treatment with an anterior pituitary-like substance. McLellan [42] recommended a preoperative course of six injections to enlarge the structures and a postoperative course of twelve injections to help prevent

38. Bevan, A. D.: Ann. Surg. **90**:847, 1929.

39. Drake, C. B.: Spontaneous Late Descent of Testis, J. A. M. A. **102**:759 (March 10) 1934.

40. Williams, P.: Lancet **1**:426 (Feb. 22) 1936.

41. Harris, F. I.: Am. J. Surg. **27**:447, 1935.

42. McLellan, E.: Lancet **1**:999 (May 2) 1936.

testicular atrophy. Cabot [43] said he believed that watchful waiting is respectable only because of its antiquity. He advised operating on boys before they are 9 and recommended the use of gonadotropic substance for those between the ages of 3 and 7. Burdick and Coley [44] have reported a series of 537 orchidopexies; 50 per cent were satisfactory as to the resulting position of the organ, and 15 per cent of the testicles were of normal size. Much higher percentages of surgical cure have been reported by Counsellor [2] and Walters.[45] In their large series of cases 92 or 93 per cent of the operations were successful, and, as others have mentioned, in a small number of cases an intra-abdominal testis was not suitable for surgical delivery. A mechanical method of treatment has been described by Ballinger, Elder and McDonald of Atlanta, Ga. A suction instrument had been used in their practice to enlarge the penis. Accidentally it was noted that those who had ectopic testes were benefited, and in 23 of 26 patients with inguinal cryptorchidism the testes descended into the scrotum.

Many observers have wondered about the observations at operation on patients who had been given organotherapy without success. Bevan and his associates [46] recently described their observations; some of the conditions encountered included shortness of structures, namely, of the peritoneal process, transversalis fascia, cremasteric fascia and muscle and intercolumnar fascia. In other cases the external abdominal ring was absent, or the peritoneal process was directed abnormally.

ADDITIONAL COMMENT

The observers who have used organotherapy for undescended testicles realize that this form of treatment is still in the experimental stage. Stimulation of the growth of the genitalia has been repeatedly observed in young children. There is still uncertainty as to the possible risks. Will these children who are stimulated early in life have a normal development after puberty? Geschickter and his associates [47] have reported hypertrophy of the prostate and breasts of monkeys after the administration of an extract of the urine of pregnant women, but in this study no enlargement was encountered in children. Koplin [48] has

43. Cabot, H.: South. Surgeon **4**:331, 1935.

44. Burdick, C. G., and Coley, B. L.: Ann. Surg. **84**:867, 1926.

45. Walters, W., and Thiessen, N.: Proc. Staff Meet., Mayo Clin. **10**:9, 1935.

46. Thompson, W. O.; Bevan, A. D.; Hecke, N. J.; McCarthy, E. R., and Thompson, P. K.: Endocrinology **21**:220, 1937.

47. Geschickter, C. F.; Lewis, D., and Hartman, C. G.: Am. J. Cancer **21**: 828, 1934.

48. Koplin, H.: Glycosuria Caused by Administration of Antuitrin-S for Bilateral Undescended Testes, J. A. M. A. **106**:374 (Feb. 1) 1936.

observed glycosuria after treatment, but Dorff [49] did not find a trace of glycosuria in 60 patients under active treatment.

Moore [50] has definitely clarified the effect of position on the testicle. He stated his belief that thermal factors play a prominent rôle in the causation of atrophy. He has found that when a testis is transplanted into the abdomen it uniformly loses the function of spermatogenesis yet regains it when replaced in the scrotum. The germinal epithelium undergoes degeneration while in the abdomen, but the interstitial cells seem to be unaffected. Wangensteen [51] confirmed Moore's work and in a series of experiments on man, the dog, the pig, and the horse failed to find mature spermatogenesis in the undescended testicle. Cooper [52] has made a histologic study of the retained testis in children; in boys over 3 years of age there usually were anatomic defects, such as an increase in the stroma and a reduction in the number and size of the tubules. In his study he observed that the farther the descent, the more the testis resembled the scrotal testis. A unique clinical study of spermatogenesis in cryptorchidism has been made by MacCollum.[53] Eighty-nine cryptorchid men were observed, and the author concluded that their fertility was poor. There was definite fertility in 77 per cent of those operated on, but it was present in only 10 per cent of those who had not been subjected to orchidopexy.

In 1934 Collip [54] studied animals which had been given a large amount of gonadotropic extract over a long period. He said he thought that the long continued administration of the gonadotropic extract from the urine of pregnant women leads to the formation of substances inhibitory to the action of this extract and that passive resistance to the extract may be produced by the administration of a serum obtained from animals which have been given injections of gonadotropic substance for a long time. This observation might well be used to explain the results noted in a few patients who have had temporary genital stimulation followed by a refractory period.

At present in the literature many problems are described that justify further investigation. Certainly the fertility of these patients deserves

49. Dorff, G. B.: Glycosuria from Treatment with Anterior Pituitary-Like Hormone for Imperfectly Developed Testis, J. A. M. A. **106**:1111 (March 28) 1936.

50. Moore, C. R.: Anat. Rec. **24**:383, 1923.

51. Wangensteen, O. H.: The Undescended Testis: An Experimental and Clinical Study, Arch. Surg. **14**:663 (March) 1927; Surg., Gynec. & Obst. **54**: 219, 1932.

52. Cooper, E. R. A.: J. Anat. **64**:5, 1929.

53. MacCollum, D. W.: Clinical Study of Spermatogenesis of Undescended Testicles, Arch. Surg. **31**:290 (Aug.) 1935.

54. Collip, J. B.: Proc. Soc. Exper. Biol. & Med. **32**:544, 1934.

protection, and, in the minds of many, the complication of a malignant process in the undescended testicle calls for serious consideration. Rea [55] found a 9.9 per cent incidence of cryptorchidism among 1,371 patients with a malignant condition of the male sex gland. If the incidence of cryptorchidism in general is considered, it is seen that the ectopic testis is involved by a malignant process fifty times more frequently than the normally situated testis.

In conclusion we realize that there are many questions still to be settled. But severe criticism is gradually changing to justifiable skepticism, and there is realization by many that the problem of cryptorchidism is not entirely medical or surgical but a combination.

55. Rea, C. E.: Am. J. Cancer **15**:2646, 1931.

SCLEREMA NEONATORUM (SUBCUTANEOUS FAT NECROSIS)

JOHN F. McINTOSH, M.D.

THEODORE R. WAUGH, M.D.

AND

S. GRAHAM ROSS, M.D.

MONTREAL, CANADA

There are two conditions in young infants which may properly be called sclerema. In early usage the term was probably employed to designate a diffuse hardening of the subcutaneous tissues occurring in weakly or marasmic infants, not necessarily new-born. It is a terminal condition, somewhat rare, sometimes seen as a complication in serious infantile diseases. For this entity the term "preagonic induration" has been suggested.

The second condition, to which the term "sclerema neonatorum" may properly be applied, becomes evident within the first few weeks of life and usually disappears after three or four months. The lesions consist of sharply defined areas of induration, attached to the skin but not to the deeper tissues and affecting the back, the buttocks, the shoulders, the cheeks and the calves of the legs. The skin is frequently livid. Softening and fluctuation have been observed and occasionally formation of cysts. The general health is not impaired. For this condition there is a growing tendency to use the pathologic term "subcutaneous fat necrosis."

For the first description of the disease (1718), we are indebted to the Swedish author Usenbenzius.[1] The name "sclerema" occurred in the literature for the first time in 1812, when Chaussier [2] used it but in the form *sclérôme*. In its original spelling it is clear that it means "hard swelling" or "induration." Many variations of the word have been used by French, German, Italian and Spanish authors; the modern English spelling, "sclerema," is one of the Italian forms.

The unfortunate inclusion of "edema neonatorum" among the diseases for which the term "sclerema" is now used and the confusion which resulted therefrom date from the work of the French author

---

From the Department of Medicine and the Subdepartment of Pediatrics, McGill University Clinic, Royal Victoria Hospital, and the Department of Pathology, McGill University.

1. Usenbenzius, J. A.: Partus octimestris vivus, frigidus et rigidus, Acad. nat. curios. ephem. **30**:62, 1722.

2. Chaussier, cited by Ballantyne, J. W.: The Diseases and Deformities of the Foetus, Edinburgh, Oliver & Boyd, 1895.

Andry [3] in 1788. The distinction between edema of the new-born and sclerema was clearly made in Billard's textbook as early as 1827. Nevertheless, some authors prefer to include the two conditions in a common grouping even today.

The confusion of sclerema with scleroderma seems to have begun with Bouchut,[4] who in 1873 maintained that sclerema in infants and scleroderma in adults were the same disease.

When we turn to consider the pathogenesis of sclerema, it is hardly profitable to review the earlier authors. The first definite light on the subject came from Langer's [5] analysis of fat in adults and in new-born infants. Langer found 65 per cent oleic acid in the latter and 86 per cent in the former. Knöpfelmacher [6] confirmed this difference and showed that the oleic acid content of the subcutaneous fat increased gradually from birth until the end of the first year. There was a corresponding gradual lowering of the melting and of the solidifying point of the fat. From his studies Knöpfelmacher came to the conclusion that sclerema could not develop after the age of 6 months.

This difference between the fat of new-born children and that of older persons has been amply confirmed by many investigators. One may mention Thiemich,[7] Jaeckle,[8] Miura,[9] Sarvonat,[10] Channon and Harrison [11] and Kohnstam and Herbert.[12] These studies make it clear why new-born infants readily suffer a hardening of their subcutaneous fat. The melting point of their fat is actually higher than the normal body temperature.

---

3. Andry, C. L. F.: Recherches sur l'endurcissement du tissu cellulaire des enfants nouveaux-nés, Hist. Soc. roy. de méd. **7**:207-220, 1784-1785; Paris, P. D. Pierres, 1788.

4. Bouchut, E.: Traité pratique des maladies des nouveau-nés, des enfants à la mamelle, et de la seconde enfance, ed. 5, Paris, J. B. Baillière, 1867.

5. Langer, L.: Ueber die chemische Zusammensetzung des menschlichen Fettes in verschiedenen Lebensaltern, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **84**:94-109, 1881; Beitrag zur Kenntnis des Sclerema neonatorum, Wien. med. Presse **22**:1375, 1881.

6. Knöpfelmacher, W.: Untersuchungen über das Fett im Säuglingsalter und über das Fettsclerem, Jahrb. f. Kinderh. **45**:177-203, 1897.

7. Thiemich, M.: Zur Kenntnis der Fette im Säuglingsalter und Fettleber bei Gastroenteritis, Ztschr. f. physiol. Chem. **26**:189-217, 1898.

8. Jaeckle, H.: Ueber die Zusammensetzung des menschlichen Fettes. Ein Beitrag zur Analyse der Fette, Ztschr. f. physiol. Chem. **36**:53-84, 1902.

9. Miura, S.: The Chemical Constituents of the Subcutaneous Fat Tissue in Sclerema Neonatorum, Hifubyog. kiu Hiniokibyog. Zasshi **5**:412-419, 1905.

10. Sarvonat, F.: Sur un cas de sclérème des nouveau-nés: Autopsie, étude chimique de la graisse, Arch. de méd. d. enf. **9**:22-31, 1906.

11. Channon, H. J., and Harrison, G. A.: The Chemical Nature of the Subcutaneous Fat in the Normal and Sclerematous Infant, Biochem. J. **20**:84-92, 1926.

12. Kohnstam, G. L. S., and Herbert, F. K.: Sclerema Neonatorum and Its Relation to Fat Necrosis, Arch. Dis. Childhood **2**:349-357, 1927.

This specific property of the fat of the new-born child may be considered as a predisposing factor, common to all infants, whether sclerematous or not. We may now inquire whether there is a difference between the fat in sclerematous and that in normal infants. Knöpfelmacher concluded that the composition of the subcutaneous fat of sclerematous children was normal for their age. Harrison and McNee,[13] on the other hand, on the basis of the melting point, maintained that there is a deficit of olein in the fat of sclerematous subjects. Their contentions found support in the data given by Siwe.[14] Bayer [15] went a step further. He did not admit that new-born infants are predisposed to sclerema on account of the chemical characteristics of their fat but expressed the belief that the composition of their fat is similar to that of adult fat and shows alterations only in sclerema. He regarded the disease as caused by a specific decrease in the olein content of the subcutaneous tissues. Thiemich,[7] Sarvonat [10] and Chen [16] denied any chemical difference between the fat of normal and that of sclerematous infants. Examination of the literature does not settle the matter. When differences in the iodine number have been found, they have been relatively small. The differences in melting point are of doubtful significance.

Thiemich [7] has made an interesting commentary on the high melting point of the subcutaneous fat of new-born infants. It is well known that perirenal fat has a higher melting point than superficial fat. During intra-uterine life the fetus lays down subcutaneous fat that has a high melting point. After birth this fat gradually becomes altered as the skin is subjected to different climatic conditions. These views are in agreement with the findings of Terroine and his associates [17] who have shown that the iodine number of a fat is in inverse relationship to the temperature at which it is synthesized.

The older authors, naturally, believed that cold was an important factor in the production of sclerema. This theory was supported by

13. Harrison, G. A., and McNee, J. W.: An Investigation of Sclerema Neonatorum, with Special Reference to the Chemistry of the Subcutaneous Tissues: I. With a Histological Report, Arch. Dis. Childhood **1**:63-84, 1926. Harrison, G. A.: Sclerema Neonatorum: II. With Special Reference to Chemistry of Subcutaneous Tissues, ibid. **1**:123-140, 1926.

14. Siwe, S. A.: Zur Pathogenese der Adiponecrosis subcutanea (Sclerodermia neonatorum), Acta path. et microbiol. Scandinav., supp. 16, 1933, pp. 438-459.

15. Bayer, R.: Ueber das Sclerema neonatorum, Verhandl. d. deutsch. path. Gesellsch. **12**:305-308, 1908.

16. Chen, T. T.: A Chemical Study of Sclerema Neonatorum, Nat. M. J. China **16**:360-364, 1930.

17. Terroine, E. F.; Bonnet, R.; Kopp, G., and Vechot, J.: Sur la signification physiologique des liaisons éthyléniques des acides gras, Bull. Soc. chim. biol. **9**:605-620, 1927.

certain clinical observations, while the chemical studies just outlined gave it a logical basis. One of the best examples of the effect of cold is a case reported by Cohen.[18] In that case, necrosis of the fat in the female breast was produced by the application of an ice-bag. Histologic examination of the tissue showed a picture similar to that found in sclerema neonatorum. Further evidence on this point was supplied by Lemež,[19] who by chilling produced experimentally in infants lesions which were clinically indistinguishable from sclerema. Lemež' article made it clear that chilling may be a factor in the etiology of sclerema and in exceptional cases may be the chief factor, although usually it is a minor one.

The next step in advance was the study of the histologic picture of sclerema. An early histologic description of the lesions is that of Fabyan,[20] which was notable as the first American contribution on the subject. He described a central area with loss of structure, surrounded by a zone showing cellular infiltration along the connective tissue septums and radiating lines, doubtless due to spaces left by "dissolved fatty acid crystals." Multinucleate giant cells were also noted. Triboulet and his co-workers [21] gave a similar description in 1912. Fabyan's article is important as the source of a fresh point of view and a new name for the condition. Since the condition which he described resembled the fat necrosis of pancreatitis, he published his report of the case as one of "Disseminated Subcutaneous Fat Necrosis." When Bernheim-Karrer [22] published his paper in 1922 he made use of Fabyan's term to designate sclerema. This article is particularly notable. It is credited with clearing up the difference between true scleroderma and sclerema, and it marks the end of the use of the term "scleroderma neonatorum" as a name for the latter and the adoption of the term "adiponecrosis subcutanea neonatorum," which is now in general use in continental Europe.

It is now generally agreed that obstetric trauma is the most important precipitating factor. This theory was mentioned by Cruse [23] in

18. Cohen, I.: Traumatic Fat Necrosis of the Breast, J. A. M. A. **80**:770-771, 1923.

19. Lemež, L.: Beitrag zur Pathogenese der subcutanen Fettgewebsnekrose Neugeborener (sog. Sclerodermia neonatorum) an der Hand einer Kältereaktion des subcutanen Fettgewebes bei Neugeborenen und jungen Säuglingen, Ztschr. f. Kinderh. **46**:323-369, 1928.

20. Fabyan, M.: Disseminated Subcutaneous Fat Necrosis Occurring in an Infant Without Other Lesions, Bull. Johns Hopkins Hosp. **18**:349-351, 1907.

21. Triboulet, H.; Ribadeau-Dumas, L., and Debré, R.: Sclérème adipeux en plaques, Jahrb. f. Kinderh. **77**:366-367, 1913; Bull. Soc. de pédiat. de Paris **14**: 199-208, 1912; Ann. de méd. et chir. inf. **16**:389-396, 1912.

22. Bernheim-Karrer, J.: Ueber subkutane Fettgewebsnekrosen beim Neugeborenen, Schweiz. med. Wchnschr. **52**:12-15, 1922.

23. Cruse, P.: Ueber Sclerodermie bei Säuglingen. Jahrb. f. Kinderh. **13**:35-48, 1879.

1878. It is supported by cases such as that of Estienny,[24] who described a lesion's developing in the cheek, at the site of application of the blade of the obstetric forceps. It is recognized that the fat necrosis of the female breast which occasionally develops after trauma and which was described by Lee and Adair [25] has a similar mechanism. The traumatic theory has been substantiated experimentally by Farr [26] in the pig and by Lemež [19] in infants.

There is still a minority among commentators on the subject who refuse to accept the traumatic theory. Gray,[27] for instance, expressed the belief that all the evidence is against it, and he cited the occurrence of the disease congenitally, the relative rarity of the condition, the latent period between birth and the development of the lesions and their symmetrical distribution. His fifth point, the supposed association of traumatic fat necrosis with saponification, rests entirely on histologic evidence; no chemical analyses of the fat have been reported in cases of subcutaneous fat necrosis in adults.

The nature of the fatty crystals has lately become a subject of investigation. Langer [5] noted crystals in fetal fat and assumed them to be fatty acids. The same assumption has been made for scleremátous fat by Fabyan,[20] Harris,[28] Farr,[26] Keilmann [29] and Harpøth.[30] Smith [31] in 1918 presented figures for the acid value of scleremátous fat which would tend to confirm that opinion. Smith's values are so much higher than those reported by others that Gray [27] expressed the belief that postmortem hydrolysis must have taken place in Smith's case.

Schultz,[32] in 1924, seems to have been the first to recognize the crystals as neutral fat. Harrison and McNee,[13] apparently unaware of Schultz' work, came to the same conclusion in 1926. Their opinion

---

24. Estienny, E.: Cytostéatonécrose sous-cutanée du nouveau-né, Bull. Soc. d'obst. et de gynéc. **22**:711-712, 1933.

25. Lee, B. J., and Adair, F. E.: Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, Ann. Surg. **72**:188-195, 1920; A Further Report on Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, Surg., Gynec. & Obst. **34**:521-531, 1922.

26. Farr, C. E.: Ischemic Fat Necrosis, Ann. Surg. **77**:513-523, 1923.

27. Gray, A. M. H.: Sclerema Neonatorum, Arch. Dermat. & Syph. **14**:635-654 (Dec.) 1926; On the Identity of Adiponecrosis Subcutanea Neonatorum with Sclerema Neonatorum, Brit. J. Dermat. **45**:498-506, 1933.

28. Harris, in discussion of Lieberthal, D.: Sclerema Neonatorum and Scleroderma, J. Cutan. Dis. **36**:29-34, 1918.

29. Keilmann, K.: Circumscripte, symmetrische Fettsklerose im Säuglingsalter (die sogenannte Sklerodermie), Ztschr. f. Kinderh. **33**:298-307, 1922.

30. Harpøth, H.: Necrosis adiposa neonatorum, Acta pædiat. **15**:259-266, 1934.

31. Smith, C. S.: Chemical Changes in the Subcutaneous Fat in Sclerema Neonatorum, J. Cutan. Dis. **36**:436-440, 1918.

32. Schultz, A.: Ueber die sogenannte Säuglingssclerodermie, Centralbl. f. allg. Path. u. path. Anat. **35**:243, 1924.

was based on careful microscopic studies of the solubility of the crystals, on their staining with certain reagents and on determination of the acid value of the fat. When slightly warmed, the crystals were soluble in ether, in purified petroleum benzine, in acetone and in pyridine, slightly soluble in alcohol, in acid and in alkaline alcohol, and insoluble in water and in acid and alkali one-tenth normal in strength. These are the typical solubilities of a neutral fat.

Harrison and McNee's opinion as to the chemical nature of the crystals has been confirmed by Kohnstam and Herbert [12] and by Siwe.[14] The former authors admit that Harrison and McNee's acid values are a little higher than those of their controls and recognize that histologic studies indicate hydrolysis in some cases.

To explain the presence of supposed fatty acids in the subcutaneous tissues, certain authors [33] have raised the question of the action of enzymes. The source of these hypothetic enzymes has been attributed variously to the parotid gland, the pancreas, the leukocytes, the subcutaneous tissues and the blood serum. Bernheim-Karrer [33b] calls attention to the work of Wohlgemuth and Yamasaki,[34] who recognized a lipase in the fat of subcutaneous tissue. These authors, we must point out, made use of the tributyrin method. It has been shown by Cherry and Crandall [35] that the enzyme which splits tributyrin is distinct from that which splits triolein. Demonstration of the presence of the former cannot be taken to indicate the presence of an enzyme which will split body fat. There is no record in the literature of any study of the enzymes actually present in sclerematous tissue.

Other opinions have been expressed as to the nature of the crystals. Thus, Lecène and Moulonguet [33a] stated that they are soaps, while Carol and van der Zande [36] described them as cholesterol esters. Harrison and McNee [13] originally thought of cholesterol esters, because the crystals in sclerematous tissues were doubly refractile. They gave up this view when they found that crystals of pure palmitin were similarly aniso-

33. (*a*) Lecène, P., and Moulonguet, P.: La cystostéatonécrose ou saponification intracellulaire du tissu cellulo-adipeux sous-cutané, Ann. d'anat. path. méd.-chir. **2**:193-214, 1925. (*b*) Bernheim-Karrer, J.: Ueber subcutane Fettgewebsnekrosen beim Neugeborenen, Ztschr. f. Kinderh. **42**:658-667, 1926. (*c*) Fabyan.[20] (*d*) Estienny.[24] (*e*) Harpøth.[30]

34. Wohlgemuth, J., and Yamasaki, Y.: Ueber die Fermente in der Haut, Klin. Wchnschr. **3**:1113-1114 (June 17) 1924.

35. Cherry, I. S., and Crandall, L. A.: The Specificity of Pancreatic Lipase: Its Appearance in the Blood After Pancreatic Injury, Am. J. Physiol. **100**:266-273, 1932.

36. Carol, W. L. L., and van der Zande, F.: Adiponecrosis subcutanea neonatorum, Nederl. tijdschr. v. geneesk. **2**:1317-1328, 1925; Acta dermat.-venereol. **7**:180-200, 1926.

tropic. They confirmed their finding by microchemical tests, which showed no cholesterol.

Quantitative chemical determinations of the cholesterol in sclerematous fat, made by Harrison and his co-workers and by Siwe,[14] gave values varying from 1.34 to 6 per cent. These values were higher than those obtained in control determinations on normal tissue, but much higher values would have been expected if the crystals had consisted of cholesterol or its esters.

Deposition of calcium and phosphorus occurs in sclerematous lesions. Chemical determinations of these elements have been reported by Harrison and McNee[13] and by Kohnstam and Herbert.[12] Morse[37] reported a case in which there were subcutaneous fat necrosis and deposits of calcium which were visible in roentgenograms. Bernheim-Karrer[38] gave five other references to calcification in his recent paper. There is still relatively little information as to the ultimate fate of the deposits of calcium. In one of Harrison and McNee's cases the calcified patches regressed and disappeared from roentgenograms within nine months. In Morse's case, however, they were visible when the patient reached the age of 3½ years. Unfortunately, the early history of this case was obscure.

In recent years the clinical concept of nonpancreatic fat necrosis has been extended in two directions. Kohnstam and Herbert[12] and de Bruin[39] have observed necrosis of the perinephric fat. De Bruin has also observed cases of congenital subcutaneous fat necrosis.

REPORT OF A CASE

A., a girl aged 25 days, was admitted to the pediatric service of the Royal Victoria Hospital on Nov. 25, 1935, on account of subcutaneous lesions to be described. She had been born November 1, prolapse of the cord having necessitated delivery by high forceps. Her condition had been considered poor. Her irritable condition, and her failure to take feedings raised the question of intracranial hemorrhage. Roentgen examination revealed fracture of the skull in the occipital region. Lumbar puncture showed clear fluid under increased pressure. After the puncture, improvement took place. About the eleventh day a reddened area developed in the midscapular region, which went on to induration and then to softening and fluctuation. Smaller areas appeared in the shoulders and the external surfaces of the upper part of the arms. The fluctuating area was aspirated on November 12. The material obtained was yellowish and semifluid. A biopsy specimen was removed on November 21.

---

37. Morse, J. L.: Calcification of the Skin in a Child, Tr. Am. Pediat. Soc. **33**:332-336, 1921.

38. Bernheim-Karrer, J.: Ueber subcutane Fettgewebsnekrosen beim Neugeborenen, Ztschr. f. Kinderh. **55**:695-701, 1933.

39. De Bruin, M.: Observations on Subcutaneous Fatty Necrosis in Newborn: Case, Nederl. tijdschr. v. geneesk. **1**:1221-1229 (March 9) 1929.

On admission to the pediatric service the child weighed 4,250 Gm. and appeared well nourished. She was afebrile. In the center of the back was a livid indurated area 1 by 2 inches (2.5 by 5 cm.), traversed by a recent surgical incision. There were three small nodules on the left side of the neck, each the size of a dime, and one over the upper part of each arm, the size of a 50 cent piece. The nodules were discrete and flat. The larger ones showed central softening and appeared to be cystic. One of these was aspirated on December 3, and the contents were used for chemical examination.

On December 3 a specimen of blood was taken, which gave the following values on analysis:

Iodine number of fatty acids.....128
Cholesterol in the plasma (colorimetric).....125 mg. per hundred cubic centimeters
Total fatty acids, as tripalmitin, in the plasma.....253 mg. per hundred cubic centimeters

The child's progress was favorable. When she was discharged, on December 12, the subcutaneous lesions were still present.

The child was brought to the outpatient department, where the progress of the lesion was observed from time to time. Roentgen examination on December 29 revealed no calcification in the soft tissues of the upper extremities. There was a fracture of the right clavicle, with formation of callus. A month later, however, a faint shadow was visible in the soft part of the left arm, in the region of the insertion of the deltoid tendon. On April 2, 1936, a well marked ringlike shadow was seen in the same position, and a faint shadow was correspondingly placed on the right arm. On November 19 a hard subcutaneous nodule, of about the diameter of a 10 cent piece, was still palpable at the insertion of the left deltoid, and roentgen examination showed a ringlike shadow in the same area. The other lesions were no longer palpable.

Histologic Studies.—The specimen for biopsy removed from the back consisted of a fusiform section of skin and subcutaneus tissue. By examination of the cut surface of the mass the dermis could be clearly differentiated grossly from the underlying subcutaneous tissue, in which the fat had become transformed into a chalky white, rather lardaceous-appearing material.

Histologic sections were prepared from fresh frozen material and by the usual paraffin-embedding method. They were stained in various ways. They showed the epiderm and the corium to be relatively normal. In the subcutaneous tissue a marked change had taken place in the fat cells. This was due to the presence of crystals (fig. 1). Toward the center of the lobules the change was less obvious, though the crystals were present at that point, but near the interlobular septums the fat cells became smaller and irregular, and the crystals became more numerous, until in some areas they appeared to replace the fatty material completely. Where scarce, these crystals were independent, small needle-like colorless structures. Where more abundant, they tended to lie in tufts, radiating from a central focus. They did not appear to take a scarlet red stain for fat in frozen sections, but in some areas they showed a slight brownish pigmentation. Crystals were present in the few fat cells in the corium, though not as numerous there as in the subcutaneous areas.

Apparently as a response to this change in the fatty tissue, there was a marked widening of the interlobular septums (fig. 2). This was due to a fibroplastic proliferation with a certain amount of cellular exudate and the formation of numerous foreign body giant cells which wrap themselves about the crystals (fig. 3). This reaction extended inward from the perivascular spaces toward the

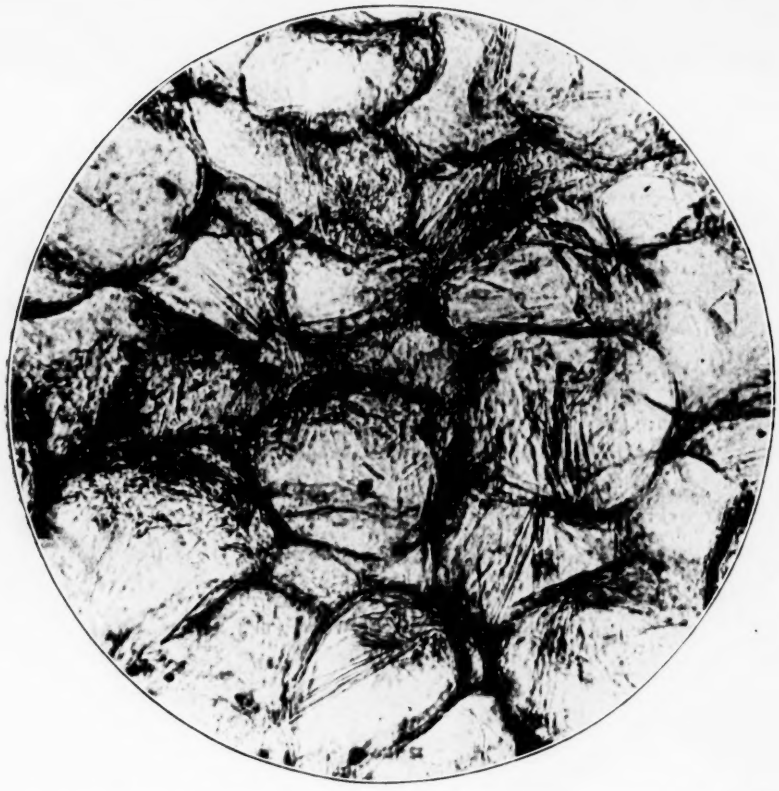

Fig. 1.—Section of fresh tissue, showing fine needle-like crystals in radiating arrangement (× 130).

Fig. 2.—Skin and subcutaneous tissue, showing disappearance of fat vacuoles at periphery of lobules and along vascular channels (× 14).

center of the lobules. In some areas the fat was almost completely replaced by this peculiar proliferative reaction.

Special stains and tests for solubility indicated that the crystals were probably those of neutral fat.

Chemical Examination.—The sample available for examination amounted to about 0.4 Gm. of creamy semifluid material. It was weighed, extracted with a mixture of hot alcohol and ether and filtered. The total fatty acids in the filtrate were determined by the titrametric method of Stoddard and Drury.[40] Cholesterol was estimated according to the colorimetric method of Bloor, Pelkan and Allen.[41] The iodine value of the fat was determined by Rosenmund and Kuhnhenn's [42]

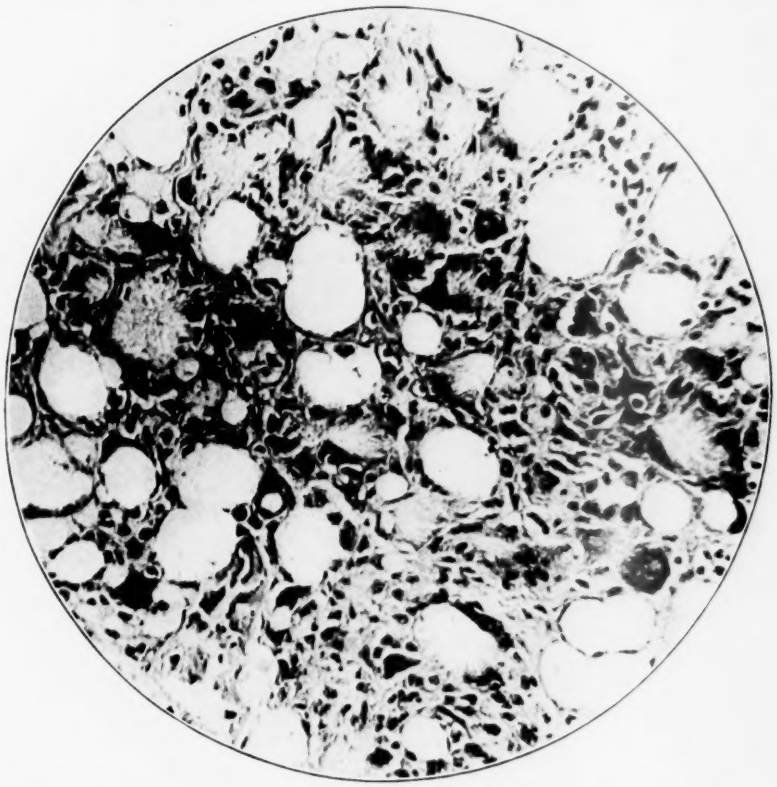

Fig. 3.—Disappearance of many fat vacuoles with foreign body giant cell reaction. Crystals have been dissolved by process of embedding, but their former location is obvious from arrangement of tissue (× 150).

---

40. Stoddard, J. L., and Drury, P. E.: A Titration Method for Blood Fat, J. Biol. Chem. **84**:741-748, 1929.

41. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, J. Biol. Chem. **52**:191-205, 1922.

42. Rosenmund, K. W., and Kuhnhenn, W.: Eine neue Methode zur Jodzahlbestimmung in Fetten und Oelen unter Verwendung von Pyridinsulfatdibromid, Ztschr. f. Untersuch. d. Nahrungs.- u. Genussmittel **46**:154-159, 1923.

method. The lipase content of a sample of the original material was determined by the method of Cherry and Crandall.[35] An extract of the material was prepared by the use of the usual mixture of alcohol and ether, and the acid equivalent was determined by titration. From this figure and the fatty acid content of the material the acid value of the fat was calculated. Unsaponifiable material was ignored in the calculations.

Material from Softened Sclerematous Area	
Total fatty acid content	17 per cent
Cholesterol content	Traces
Iodine absorbed	0.109 Gm. per gram of sample
Lipase (olive oil substrate)	None

COMMENT

The conclusion of Schultz [32] and of Harrison and his co-workers [43] that the fats, and especially the crystals, present in sclerematous tissue are composed mainly of neutral fats was based on such thorough work that it appears irrefutable. Since it has not been universally accepted, however, it has seemed worth while to report the histologic and chemical

Results of Analysis of Sclerematous and Normal Fat by Various Investigators

	Fat of Sclerematous Subjects			Fat of Control Subjects			
	Iodine Value	Acid Value	Total Cholesterol, Percentage	Iodine Value	Acid Value	Total Cholesterol, Percentage	Comment
Smith [31]	44-48	163	....	....	....	....	
Harrison and McNee [13]	42.1-52.0 45.5-54.0	.... 5.4-9.0	0.45* 1.5*-6.0*	45.7-57.5 53.8-68.7	.... Nil-2.7	0.82* 0.18-0.26	Melted fat Ether extract
Kohnstam and Herbert [12]	46.7	2.7	....	....	....	....	
Siwe [14]	39	7.2	1.34*	49-63	2.3-5.1	0.29*-0.42*	
Present case	64	3.2	Trace	....	....	....	Lipase absent

* Determinations of cholesterol were made by the digitonin method.

findings in the present case in support of this view. For purposes of comparison, figures from the literature and those for the case here reported are collected in the table. The figures show clearly that cholesterol and its esters can be ruled out at once. The acid values, except those in Smith's [31] case, show that the fatty acids cannot be present as soaps or as free acids. His figures are at variance with the rest, perhaps on account of postmortem changes.

The view that free fatty acids are present in negligible amounts, if at all, in sclerematous tissue is supported by the absence of lipase acting on triolein. This finding is not at variance with the work of Wohlgemuth and Yamasaki.[34] The enzyme found by them in subcutaneous and other fatty tissues was demonstrated by its action on tributyrin. Our finding is similar to that reported by Cherry and Crandall [35] for normal dog's blood, which was found to contain an enzyme capable of splitting tributyrin but not triolein.

43. Channon and Harrison.[11] Harrison and McNee.[13]

Another point in Harrison's work requires confirmation. He found that, whereas the crystals from the fat of sclerematous infants melted at from 40 to 50 C. under all circumstances tried, crystals from the fat of nonsclerematous infants melted at 30 C. in frozen sections and after separation by melting. When separated by ether extraction, however, their melting point rose to from 40 to 50 C. Harrison suggested that the original difference in melting point may result from a difference in the composition of the mediums in which the crystals are suspended. If this is true, we must admit that another specific factor is at work in sclerema—something in the "medium" surrounding the crystals which alters their melting point.

CONCLUSION

1. The chief predisposing factor in sclerema, or subcutaneous fat necrosis, is the low olein content of the subcutaneous fat in the newborn child.

2. The chief precipitating factor is believed to be obstetric trauma.

3. The subcutaneous fats are altered in their physical aggregation, but not in their chemical state; they remain as triglycerides.

4. No lipase capable of hydrolyzing body fats is present in sclerematous tissue.

Case Reports

MASSIVE CERVICAL HEMANGIO-ENDOTHELIOMA IN A NEWLY BORN INFANT

CLEMENT A. SMITH, M.D.
BOSTON

A case of a rare condition, massive hemangio-endothelioma of the neck and shoulder in a newly born infant, is presented, together with the observations at operation and postmortem examination.

Cystic hygroma is the usual cause of congenital enlargement of this region, and that condition has been diagnosed seventeen times in the past fifteen years at the Children's Hospital. A hemangio-endothelioma of this region has never been observed at the Children's Hospital, nor has it been diagnosed prior to the present case in any of the 40,000 children born at the Boston Lying-in Hospital.

REPORT OF A CASE [1]

On April 28, 1936, a 19 year old primipara after an uneventful pregnancy and a normal labor gave birth to a 6 pound, 6 ounce (2,892 Gm.) boy, three weeks before the expected date of confinement. The parents were Russian Jews. There was no family history of congenital anomalies or neoplastic diseases. Because of the presence of the tumor, some difficulty was encountered in delivering the shoulders, but the infant cried immediately and required no resuscitation.

A large mass was at once noticed over the left shoulder, obliterating the angle of the neck. It extended from the left clavicle posteriorly (fig. 1). The skin was thin, smooth and faintly reddish purple, particularly over the middle of the tumor. The mass was firm, except for several fluctuant areas, and did not transmit light. Except for the presence of the tumor, the physical examination showed no abnormality. The roentgenogram (fig. 2) demonstrated a dense mass of soft tissue involving the left shoulder, compressing the left side of the chest and displacing the scapula and humerus backward and downward. The left lung appeared compressed. The right lung showed nothing abnormal.

On May 1, three days after birth, operation was performed with the patient under ether anesthesia. It was planned to remove tissue for biopsy, but the tumor was dissected out so easily that excision was performed. The tumor was exposed immediately beneath the platysma myoides muscle and was shelled out with ease. The base lay directly over the brachial plexus, and a portion of the capsule was

From the Boston Lying-in Hospital, the Children's Hospital, Boston, and the Departments of Obstetrics and Pediatrics of the Harvard University Medical School.

1. Surgical findings are reported through the courtesy of Dr. W. E. Ladd. Dr. Sidney Farber supplied the pathologic report.

not removed from this region. At the conclusion of the operation the infant's condition was fair, and he was immediately returned to the ward. Bleeding had not been excessive. Two hours later his pulse and respiration suddenly became weak and rapid, and death occurred after a few moments.

Fig. 1.—Photograph showing the external appearance of the tumor.

Fig. 2.—Roentgenogram showing compression of the left side of the chest.

The major pathologic observations were reported as follows:

"The specimen submitted from the operating room consisted of four pieces of tissue, varying in size from 4.5 to 5 cm. in greatest length, and from 0.5 to 2 cm. in greatest thickness. The tissue was soft and flabby and cystic in places, with

multiple hemorrhagic areas. On microscopic examination (fig. 3) the tissue was fairly uniform. In some areas there was a cellular fibrous tissue forming the walls of large cystic spaces, from the flattened endothelium of which numerous solid and papillary outgrowths arose. These spaces were mostly filled with red blood cells. In other areas large numbers of cells, which tended to form small lacunar spaces, comprised the body of the tumor. The cells were small and slightly spindle shaped, with fairly large, hyperchromatic nuclei. They were oval or irregular in outline. The cytoplasm of the borders was in general, poorly defined. There were numerous mitotic figures. In general there was little connective tissue stroma.

Fig. 3.—Microscopic picture of the structure of the tumor, showing capillary spaces above, cavernous spaces below and solid mass of tumor cells in the center. (Hematoxylin and eosin stains; reduced from magnification of 165 times.)

The picture was typical of a hemangio-endothelioma, consisting in part of masses of endothelial cells which were actively growing without showing evidence of intravascular extension of the tumor.

"At autopsy a diffuse terminal pneumonia of approximately twenty-four hours' duration was evident. The pneumonic picture was accompanied by a considerable amount of primary atelectasis. There was, in addition, evidence of a fairly marked degree of aspiration of material from the amniotic sac. Little except a small portion of the capsule of the tumor was found at the site of operation. The only other thing of importance observed was a caput succedaneum."

A review of the literature revealed two cases [2] in which the details of location, size, structure and histopathologic picture were similar to those in the case here reported. In both reports the potential, if not the actual, malignancy of the cellular structure was stressed.

The term hemangio-endothelioma is used here entirely descriptively, to designate a form of hemangioma with an overgrowth of the cells lining the blood spaces. The tissue was not simply a proliferation of thin-walled vessels, such as those which compose the ordinary cutaneous capillary hemangioma, though the tumor might have been considered a more cellular member of the same general group. The exact point of origin of this particular tumor was not determined, but such masses apparently share with cavernous lymphangioma or hygroma a tendency to formation at sites such as the cervical and axillary regions, where important vascular connections are laid down during fetal development. Thus, a more common location of hemangio-endothelioma is in the liver. Kunstadter [3] has collected fifteen instances of the latter process in infants. It is of interest that in a third of these cases metastases to other organs were found. This evidence, together with that of the proliferation of endothelial cells observed microscopically, indicates that such a hemangio-endothelioma of the neck should be surgically removed as soon as operation seems safe for the infant. The condition should not be confused with hygroma and other benign cervical cysts, with which considerable delay is justifiable.

In the case reported, operation was performed on the third day of life. At necropsy a considerable degree of atelectasis, diffuse bronchopneumonia and evidences of aspiration of material from the amniotic sac were found, although there had been no clinical or roentgenologic evidences of these conditions. The striking compression of the chest by the tumor may have contributed to the atelectasis. In any case, the process in the lungs, antedating the operation, must have been an unfavorable influence on the postoperative course.

SUMMARY AND CONCLUSION

An unusual case of massive hemangio-endothelioma of the neck in a newly born infant is reported.

Such a tumor is potentially malignant and demands early removal. It should be considered as a possibility in the diagnosis of congenital cervical enlargements, which are usually assumed to be benign.

---

2. Stiefel, E.: Ueber das angeborene Haemangioma simplex, Arch. f. Gynäk. **111**:370, 1919. Pettersson, A. S., and Romanus, R.: Ein Fall von Haemangioma cavernosum congenitum mit tödlichen Ausgang, Acta pædiat. **14**:417, 1933.

3. Kunstadter, R. H.: Hemangio-Endothelioma of Liver in Infancy, Am. J. Dis. Child. **46**:803 (Oct.) 1933.

ELONGATED MECKEL'S DIVERTICULUM IN A CHILD

MOE GOLDSTEIN, M.D.
Fellow in Pediatrics
AND
RICHARD W. CRAGG, M.D.
Fellow in Pathology
ROCHESTER, MINN.

Meckel's diverticulum, although it is a common anomaly, at times may exhibit some unusual features, as it did in the case we are about to report.

REPORT OF A CASE

A girl aged 5 years was admitted to the Mayo Clinic on Nov. 17, 1936, because of melena, which had been present for four and one-half years, and abdominal pain, which had been present for three years.

She was an only child. The delivery had been normal and at term. The child had been breast fed for nine and one-half months, and her development had been normal. She had had whooping cough at the age of 10 months but had not had any other illness. She had not been immunized against smallpox, diphtheria or any other disease.

When she was 6 months of age the patient had expelled a considerable amount of bright red blood from the rectum. For several days thereafter her stools had been black and had resembled tar. Five months later the patient had had a severe hemorrhage from the bowel. She was said to have been "almost exsanguinated," and blood had been administered intramuscularly. At irregular intervals from that time on, the stools had been tarry. Three weeks prior to her admission to the clinic fresh blood again had been noticed in the stools. Bowel movements had been normal. She had been taking laxatives for two years.

In November 1933, when the child was 2 years of age, she had begun to have attacks of severe abdominal pain. She had had as many as from four to six attacks daily; each attack had lasted for from fifteen to twenty minutes. The attacks had occurred during the night as well as during the day and had been of sufficient severity to awaken the child. They had not been related to the type of food ingested or to the time of her meals. Her appetite had always been good. There never had been any vomiting or hematemesis.

The rest of the history was irrelevant except for the fact that for the two months previous to her admission to the clinic her respiration had been wheezy, which had been interpreted as a manifestation of asthma.

Physical examination showed her to be fairly well developed. Her weight was 32½ pounds (14.7 Kg.); the normal weight for her height and age was 38 pounds

From the Mayo Foundation.

(17.2 Kg.). The rectal temperature was 100 F., and the pulse rate was 120 beats per minute. A few teeth were carious. The tonsils appeared to be septic. The spleen was palpable. Otherwise, the results of physical examination were normal.

Examination of the urine did not disclose any abnormality. Examination of the blood showed 84 per cent hemoglobin. The leukocytes numbered 10,100 per cubic millimeter of blood. The differential blood count showed 25.5 per cent lymphocytes, 5.5 per cent monocytes, 65.5 per cent polymorphonuclear neutrophils, 2.5 per cent eosinophils and 1 per cent basophils. The flocculation test for syphilis was negative. The intradermal tuberculin test was negative. The proctoscopic examination revealed that the rectum and the rectosigmoid appeared normal for a distance of 24 cm. from the anus.

Roentgenograms of the thorax, the stomach, the duodenum and the colon showed no abnormality.

A diagnosis of Meckel's diverticulum was made. On Nov. 21, 1936, four days after her admission to the clinic, an exploratory operation was performed. The

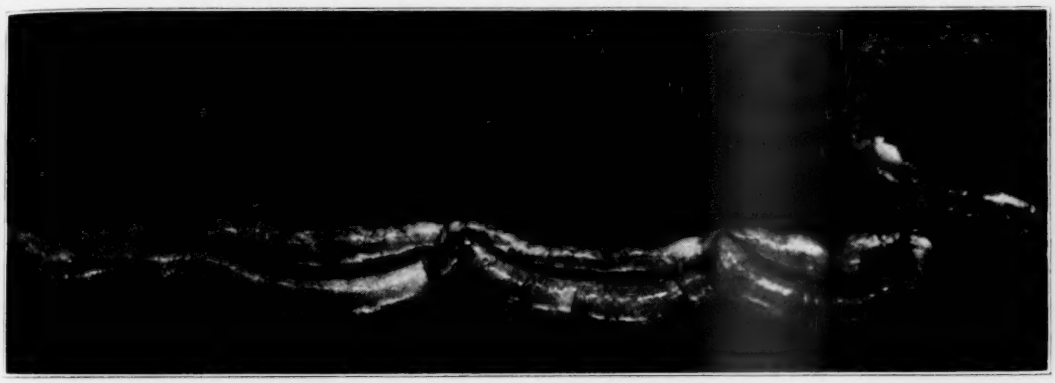

Fig. 1.—Ileum and Meckel's diverticulum.

surgeon made the following note: "The patient had a Meckel's diverticulum which measured more than 2 feet (61 cm.) in length. The distal end was buried in the mesentery. There was an ulcer of the mucosa located about 1½ inches (3.8 cm.) from that end. Because there was a common mesentery for the ileum and the diverticulum, resection of the entire diverticulum was considered impossible without removal of an equal length of ileum. An anastomosis was made between the diverticulum and the ileum at a point about 4 inches (10.1 cm.) proximal to the distal end of the diverticulum."

The child did not do well after the operation; paralytic ileus and bronchitis developed. She was placed in an oxygen tent. Various supportive measures, including two blood transfusions, were given. Her condition became progressively worse, and she died at 3 a. m. November 24, three days after the operation.

PATHOLOGIC PICTURE

Gross Examination.—Necropsy was limited to the thorax and the abdomen. Each pleural cavity contained approximately 500 cc. of flaky yellow fluid. The lower lobes of both lungs were edematous, nodular and of more than normal

consistency. The gross diagnosis of bronchopneumonia was confirmed microscopically. The abdominal cavity contained about 200 cc. of purulent fluid, and the intestinal coils were moderately distended with gas and loosely bound together by a fibrinopurulent exudate. The examination revealed no other significant findings except the anomaly to be described.

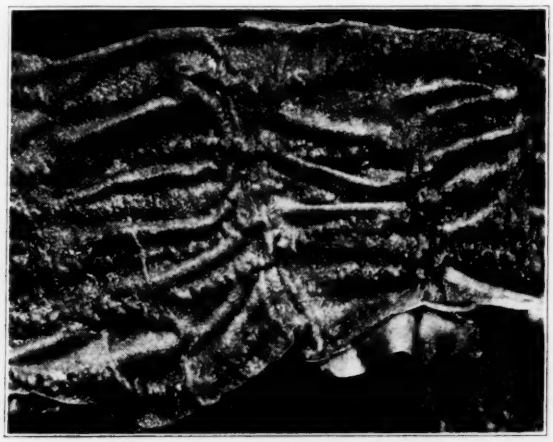

Fig. 2.—Mucosa of Meckel's diverticulum, disclosing the longitudinal rows of polypoid nodules.

Fig. 3.—Site of transition in Meckel's diverticulum, revealing the smaller segment and the ulcer.

Meckel's diverticulum originated from the mesenteric border of the ileum 45 cm. above the ileocecal valve and extended upward toward the jejunum for a distance of 66 cm. (fig. 1). Throughout the first 52 cm. of its course it was closely connected to the ileum by a common mesentery. The distal 14 cm. deviated from

the ileum toward the root of the mesentery; the tip was bound in a mass of fibrous tissue. Proximal to the place where the diverticulum was separated from the ileum there was a recent surgical anastomosis connecting the lumens of the diverticulum and the ileum. For the first 58 cm. the diverticulum had a diameter equal to that of the ileum (approximately 3 cm.), and then it narrowed abruptly to a diameter of 1 cm. From that point the diverticulum gradually became smaller, so that the distal 3 cm. resembled the vermiform appendix. When the diverticulum was opened longitudinally the wall of the proximal portion (58 cm.) was slightly thicker than that of the ileum, and the smooth mucosa was broken by multiple longitudinal rows of polypoid nodules, which varied from 2 to 4 mm. in height (fig. 2). The site of transition to the smaller, distal, portion of the diverticulum was not unlike the pylorus of the stomach; the wall was thick, but the mucosa was uneven (fig. 3). From this point to the tip the wall remained thick, and the

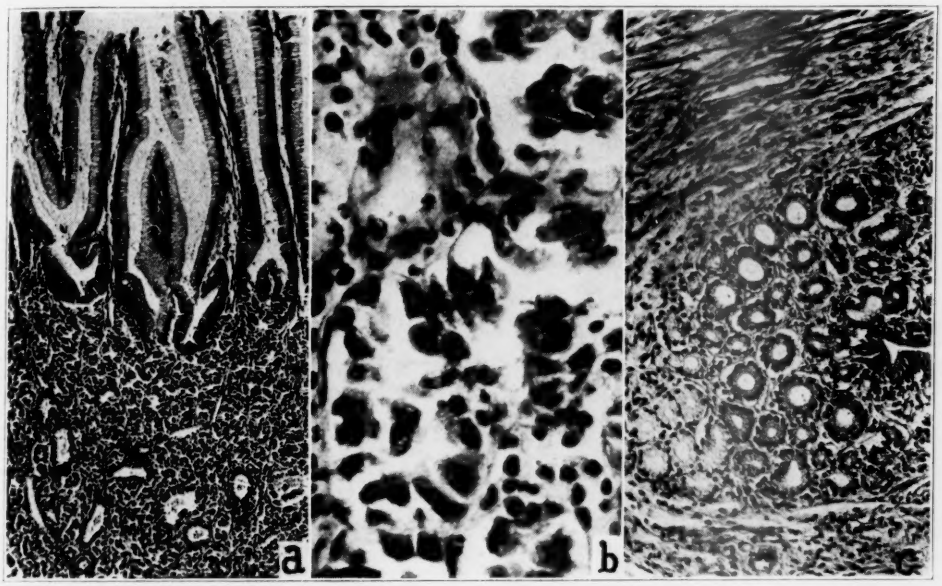

Fig. 4.—*a*, typical area of gastric mucosa (× 40); *b*, gastric glands disclosing numerous parietal cells (× 380) and *c*, Brunner glands beneath the surface epithelium in the distal segment of the diverticulum (× 40).

lumen narrowed. Three centimeters beyond this line of transition an ulcer was seen, which measured 8 mm. in diameter and 3 mm. in depth. Its walls and base were firm and white, which made it appear chronic. A search was made for a small thrombosed artery which might have been the source of the bleeding, but none could be identified grossly.

Microscopic Examination.—In order that every possible type of tissue which might be present in the diverticulum might be seen microscopically, twelve portions of the wall were removed from various regions along its course. They were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Every microscopic section taken from the proximal 58 cm. of the diverticulum revealed gastric mucosa throughout its entire length (fig. 4*a*). No evidence of any type of intestinal mucosa was observed, although many of the sections were taken from

regions which appeared grossly to be most likely to contain it. The polypoid nodules were found to be composed entirely of hyperplastic masses of gastric glands. Throughout all sections typical mucous cells were present in the surface epithelium, and the glands were made up generally of chief cells. The parietal cells were also seen in all sections, but they were more rare than is normal in the fundus of the stomach (fig. 4*b*). The muscularis mucosae was distinct, and the heavy musculature of the walls was well defined. The latter was composed of an outer longitudinal and an inner circular layer of muscle, as is seen more characteristically in the intestine than in the stomach. The wall of the distal segment (14 cm.) of the diverticulum was similar to the proximal portion, except that the submucosa and the layers of muscle were much thicker. The gastric mucosa continued to the tip of the diverticulum. However, there was one essential difference: Scattered throughout this portion, especially around the ulcer, were patches of duodenal mucosa, with typical groups of Brunner's glands lying beneath the surface epithelium (fig. 4*c*). The ulcer itself was similar to a chronic ulcer of the duodenum. Its walls and base were composed of a thick layer of dense, fibrous tissue, in which were observed many small nerve bundles and arteries. The exposed surface of the ulcer revealed a thin layer of fibrin and necrotic tissue containing masses of polymorphonuclear leukocytes and lymphocytes. At one point in the necrotic tissue there was a small artery, which was completely occluded by a partially organized thrombus.

COMMENT

This case serves to emphasize the fact that Meckel's diverticulum may be of great length. This specimen measured 66 cm. Such a large diverticulum is an unusual finding, although longer specimens have been reported. Tisdall [1] described one of 104 cm.; Pollard [2] reported one of 90 cm. in a new-born infant; in the case reported by Moll,[3] the specimen was 85 cm. in length, and Edwards [4] reported a case in which the specimen was 72.5 cm. long. Diverticula have been reported of 65 cm. (Edmunds [5]), 56 cm. (Yates [6]), 45 cm. (Abt and Strauss [7]) and 22.5 cm. (Robertson [8]).

The diverticulum in this case arose from the mesenteric border of the ileum and shared a single mesentery with the ileum. This feature,

1. Tisdall, F. F.: Unusual Meckel's Diverticulum as Cause of Intestinal Hemorrhage, Am. J. Dis. Child. **36**:1218-1223 (Dec.) 1928.

2. Pollard, Bilton: A Diverticulum Ilei of Unusual Length and Position (Card Specimen), Tr. Path. Soc. London **47**:47-48 (April 21) 1896.

3. Moll, H. H.: Giant Meckel's Diverticulum, Thirty-Three and One-Half Inches Long, Brit. J. Surg. **14**:176-179 (July) 1926.

4. Edwards, Harold: Congenital Diverticula of the Intestine, with the Report of a Case Exhibiting Heterotopia, Brit. J. Surg. **17**:7-21 (July) 1929.

5. Edmunds, Arthur, cited by Edwards.[4]

6. Yates, H. B.: A Remarkable Meckel's Diverticulum, Brit. J. Surg. **17**:456-462 (Jan.) 1930.

7. Abt, I. A., and Strauss, A. A.: Meckel's Diverticulum as a Cause of Intestinal Hemorrhage, J. A. M. A. **87**:991-996 (Sept. 25) 1926.

8. Robertson, cited by Tisdall.[1]

too, is unusual, for although Fitz [9] reported several cases in which the diverticulum was firmly attached to the surface of the ileum, it did not in any instance originate in its free aspect but arose or lay within the mesenteric insertion, and the two structures were covered by a common peritoneal investment. Some authors have said that such cases represent instances of reduplication of the small intestine. The presence of heterotopic tissue in the case reported here is proof that Meckel's diverticulum was present.

The presence of heterotopic tissue is not uncommon in Meckel's diverticulum. In the case we have reported the diverticulum was lined with a mucosa characteristic of that of the stomach throughout its entire length, except for small regions in the distal portion in which it was characteristic of duodenal mucosa. Brunner's glands appeared in these sections.

Schaetz [10] reported 50 per cent abnormal elements in thirty diverticula, including pancreatic tissue, duodenal or peptic mucosa and gastric mucosa (16 per cent). In three of eighteen cases of Meckel's diverticulum, Greenblatt, Pund and Chaney [11] found heterotopic tissue, which included gastric mucosa, pancreatic tissue and Brunner's glands. Curd [12] reported the occurrence of gastric mucosa in three of nineteen specimens studied. In one there was also pancreatic tissue. Hudson and Koplik [13] found that 67 per cent of the diverticula which they examined contained gastric mucosa. In fifty diverticula examined by Koch,[14] gastric mucosa was present in six and pancreatic tissue in two. Brown and Pemberton [15] mentioned that Carlsen, who studied one hundred and fifty-two diverticula obtained at necropsies, found that 27.6 per cent contained heterotopic tissue. In fifty-five cases of diverticulum

9. Fitz, R. H.: Persistent Omphalo-Mesenteric Remains: Their Importance in the Causation of Intestinal Duplication, Cyst-Formation, and Obstruction, Am. J. M. Sc. **88**:30-57 (July) 1884.

10. Schaetz, Georg: Beiträge zur Morphologie des Meckel'schen (Ortsfremde Epithelformationen im Meckel) Divertikels, Beitr. z. path. Anat. u. z. allg. Path. **74**:115 and 225, 1925.

11. Greenblatt, R. B.; Pund, E. R., and Chaney, R. H.: Meckel's Diverticulum: An Analysis of Eighteen Cases with Report of One Tumor, Am. J. Surg. **31**:285-293 (Feb.) 1936.

12. Curd, H. H.: Histologic Study of Meckel's Diverticulum, with Special Reference to Heterotopic Tissues, Arch. Surg. **32**:506-523 (March) 1936.

13. Hudson, H. W., Jr., and Koplik, L. H.: Meckel's Diverticulum in Children: A Clinical and Pathologic Study, New England J. Med. **206**:827-840 (April 21) 1932; cited by Hudson, H. W., Jr.: Meckel's Diverticulum in Children: Second Clinical and Pathologic Study with a Report of Thirteen Additional Cases, ibid. **208**:525-535 (March 9) 1933.

14. Koch, M., cited by Cobb.[18]

15. Brown, P. W., and Pemberton, J. deJ.: Solitary Ulcer of the Ileum and Ulcer of Meckel's Diverticulum, Ann. Int. Med. **9**:1684-1702 (June) 1936.

in which operation was performed, those authors found gastric mucosa in thirteen and jejunal mucosa in one. Duodenal glands, mucosa characteristic of the colon and tissue resembling that of the parotid gland have also been found.

In the case reported here there was a peptic ulcer in the distal portion of the diverticulum. Microscopic section revealed a thrombosed vessel in the wall of the ulcer, which may have been the source of the hemorrhage. Ulcer in Meckel's diverticulum was first reported in 1902 by von Denecke.[16] The first clinical diagnosis is said to have been made in 1927, by Ketterer.[17] Cobb,[18] in an excellent review, collected reports of ninety-eight cases of ulcer in Meckel's diverticulum and added two more of his own. Since Cobb's report, ulcer in Meckel's diverticulum has been reported by Christopher and Blessing,[19] Greenblatt, Pund and Chaney,[11] Curd [12] and Brown and Pemberton.[15] Gastric mucosa was present in sixty-six of the hundred cases collected by Cobb; in thirty-four of the cases either gastric mucosa was not found or its presence was not recorded. Fifty-five of these ulcers perforated and caused death in 36 per cent of the cases. In the forty-three cases in which the ulcer did not perforate the mortality was 12 per cent. In seventeen of the one hundred the diagnosis was correctly made before operation. Pain and hemorrhage were the most common symptoms. The sites of the ulcers varied, but the most common site was the junction of the diverticulum with the intestine.

SUMMARY

An unusual case of Meckel's diverticulum in a girl aged 5 years is reported, with the following interesting features: (1) The diverticulum measured 66 cm.; (2) it arose from the mesenteric border of the ileum and had a common mesentery with it; (3) the diverticulum contained gastric mucosa and duodenal mucosa with Brunner's glands; (4) a peptic ulcer was present in the distal tip of the diverticulum, and the classic symptoms of pain and hemorrhage were present, and (5) the occurrence of hemorrhage from the bowel and abdominal pain led to a preoperative diagnosis of Meckel's diverticulum.

16. von Denecke: Ueber die Entzündung des Meckel'schen Divertikels und die Gangrän desselben, Deutsche Ztschr. f. Chir. **62**:523-547, 1902.

17. Ketterer, E. A., cited by Cobb.[18]

18. Cobb, D. B.: Meckel's Diverticulum with Peptic Ulcer, Ann. Surg. **103**: 747-764 (May) 1936.

19. Christopher, Frederick, and Blessing, Robert: Perforated Ulcer of Meckel's Diverticulum, Am. J. Surg. **31**:556-557 (March) 1936.

PROGRESSIVE GENERALIZED (DIFFUSE) SCLERODERMA WITH SCLERODACTYLIA AND CALCINOSIS

DANIEL J. PACHMAN, M.D.

DURHAM, N. C.

On July 1, 1936, a letter concerning a child with an unusual cutaneous disease was received at the hospital. An excerpt from the letter is as follows:

"I am a roving reporter for a newspaper, with headquarters in Washington. I travel continuously over the country, and naturally I run into some odd things. The subject of this letter is something I happened onto in a city in North Carolina last February.

"The newspaper boys in this city told me I might find a feature story in a little boy there, who had a strange disease which the local doctors had not been able to diagnose. So I went out to see the child.

"The parents are extremely poor. They live in a disheveled suburb across the railroad tracks called 'Lingo City.' When I arrived the mother was out in the yard chopping wood and chewing tobacco. She is a young woman and seemingly intelligent.

"We talked a little while about the child, and she asked me if I wanted to see it. I told her yes, and we went in the house. A stench was noticeable the minute we walked through the door. She went over behind the stove to a box about a foot high, standing along the wall and covered with blankets. She raised the blankets, and there was the most horrible sight I have ever witnessed—and as a newspaper reporter for many years I have seen some pretty bad things.

"The child is now 12 years old. He was normal (even above average in health and intelligence, his mother says) until he was 2 years old. Then something started on his foot that looked like a bad sunburn. Gradually it got worse and began to spread, and at the same time his weight began to dwindle away.

"This has been going on for ten years. Today it takes a long stretch of the imagination to consider the object lying there on the box a human being. The child has no flesh at all on its body. Just skin, shrunk around the bones—or, rather, skin in some places. In others the bone is showing through. And every square inch of skin that the child does have is a running sore.

"The mother dresses the sores twice a day. It is a revolting task. The child can no longer talk, except for some slight jargon which the mother understands. It is able only to indicate to her whether it is hot or cold and to tell her when it is hurting worse than usual."

A member of the staff of the hospital visited the child and made arrangements for his hospitalization by the pediatric service of the Duke Hospital on Oct. 3, 1936.

From the department of pediatrics, Duke University School of Medicine and the Duke Hospital.

The family history was irrelevant. The father and mother were both living and well. There had been six normal pregnancies, the patient being the first child. The remaining five children were living and well. No similar condition existed in any of the relatives of the family. There was no history of contact or familial incidence of leprosy or tuberculosis.

The history of the present illness, as obtained from the parents and from hospital records, was as follows: The child appeared normal. His existence had been uneventful until he reached the age of 2 years, when he fell and broke two ribs on the right side. Shortly afterward he began to have an elevation of temperature in the afternoon, followed by night sweats, anorexia and loss of weight, which continued for a period of one year. He was then admitted to a hospital with a diagnosis of pellagra. A blood transfusion was given, and he gained weight. He was discharged one month later, considerably improved.

Fig. 1.—Patient at the time of the first examination. The torso is the size of that of a 3 year old child.

When he returned home his appetite again became poor, and the skin of his hands began to scale; the scaling areas gradually became larger, and six months later the entire surface of his skin was involved. The skin subsequently became fissured, infected and ulcerated, and then healed spontaneously after three or four weeks. This cycle of scaling, cracking, infection, ulceration, healing and scarring has been repeated constantly since the onset ten years ago. In addition, there has been marked wasting of the subcutaneous tissues and musculature, resulting in contractures of the upper and lower extremities. Between his third and his seventh year he had numerous periods of diarrhea, with from ten to twelve watery stools a day. These at times contained bright red blood. Since that time, however, his bowel movements have been normal. Two years ago, when the patient was 10 years old, his eyes became affected, and he has gradually lost his vision. At about the same time his hair began to fall out, and at present he is hairless and totally blind.

There have been some shortness of breath and moderate swelling of the abdomen at various times. He has frequently complained of pains over his entire

body and of being too warm, even in moderately cool weather. For the past few years his appetite has been good. He has been fed meats, vegetables, fruits, eggs, cereals and milk, but there has been no apparent improvement in his condition. For the past ten years he has been cared for by his parents and has had no medical treatment.

Physical examination showed a markedly emaciated, extremely distorted, underdeveloped white boy, whose torso appeared no larger than that of a 3 year old child (figs. 1 and 2). He answered questions intelligently, and, although speech was slurred, he could be understood. The skin was glistening and parchment-like.

Fig. 2.—Larger view of the patient's head and torso.

Ulcers were distributed unevenly over the entire body. Their borders were irregular and surrounded by a fungating growth of tissue. Seropurulent material exuded from the bases of some, while others were in the process of healing. The skin over the extremities was drawn tight, and both the elbows and the knees were drawn into marked acute flexion. Stumps were all that remained of the hands and the feet. In the regions of the knees, the elbows and the hips there was an abundance of fibrous tissue. Where cutaneous lesions were present small areas of bone were clearly visible. The scalp was hairless, and a large fungating crust extended up from the neck on the right to involve the ear and the periaural region. There was marked eversion of both upper and lower eyelids, and a

small amount of purulent exudate was present at both inner canthi. The scleras and corneas of both eyes, particularly the right, were cloudy. Light and dark could barely be distinguished. Acuity of hearing was not diminished, but both ears were grossly deformed and matted down, the external auditory meatus alone being distinguishable. The nose was shrunken, but the sense of smell was normal. No perforation of the nasal septum could be seen, and the mucous membrane appeared pale and was sensitive to pressure. The lips were large and everted. There were two sets of teeth, the primary incisors protruding downward and forward above the lower lip. The tongue was coated; the lower jaw was pushed back and appeared small and underdeveloped. Examination of the pharynx was not satisfactory, owing to marked limitation of motion in the temperomandibular joints. The heart was not enlarged, and no murmurs could be heard. The lungs were clear throughout. The abdomen could not be palpated satisfactorily, owing to tautness of the skin. There was no enlargement of the lymph nodes. Sensation was present over the entire body.

The blood count showed 3,100,000 red blood cells, 58 per cent hemoglobin (7.8 Gm.), 9,750 white blood cells, 65 per cent polymorphonuclear neutrophils, 1 per cent eosinophils, 1 per cent basophils and 33 per cent lymphocytes. The color index was 0.84. The blood contained, per hundred cubic centimeters, 9.4 mg. of calcium, 5.8 mg. of phosphorus, 162 mg. of cholesterol, 95 mg. of sugar and 30 mg. of nonprotein nitrogen. There were 3.1 Bodansky units of phosphatase, and the refractive index was 1.3512. The urine and the stools were normal, and the Wassermann reaction was negative. In a twenty-four hour specimen (405 cc.) of urine the total nitrogen content was 3.52 Gm., the creatine content 0.312 Gm. and the creatinine content 0.162 Gm.

Roentgenograms showed the cranial vault to be of average thickness and without localized changes or signs of increased pressure. The sella turcica was normal, and the pineal body was not calcified. The thoracic and lumbar parts of the spine showed a scoliosis concave to the left and considerable demineralization of the vertebrae. The thorax was not well expanded, but the lungs were clear. The ribs were normally developed. The bones of the upper extremities were considerably underdeveloped; the radii and ulnas were of about half the normal size. The bones of the wrists and the hands were extremely deformed and decalcified. None of the phalanges could be distinguished, but they appeared to be collapsed and decalcified rather than absent. There was extensive diffuse calcification in the soft tissues of the arms and legs. The bones of the feet were markedly underdeveloped, and changes similar to those in the hands were present. The phalanges of the toes were present but collapsed, owing to the extreme decalcification (fig. 3).[1]

A crusted lesion, together with the adjacent skin of the abdominal wall, was removed for pathologic study and culture.[2]

Microscopic sections showed a granulating ulcer beneath the fibrinous crust. In the floor of the ulcer were numerous polymorphonuclear neutrophils. No large areas of necrosis were present. More than a centimeter distant from the region denuded of epithelium, evidence of chronic inflammation was present, in the form

1. Roentgenograms were read by Drs. R. J. Reeves and W. W. Vaughn, of the department of radiology.

2. Pathologic study was made by Dr. R. D. Baker, of the department of pathology, and mycologic and bacteriologic studies by Dr. N. F. Conant, of the department of bacteriology.

of diffuse lymphocytic and large mononuclear infiltration of the dermis, as well as perivascular lymphocytic infiltration (fig. 4).

The epidermis was of about normal thickness, or possibly slightly thickened for this region. The under-surface of the epidermis was smooth, rete cones being practically absent. The keratinized layer was only moderately conspicuous, and parakeratosis was not noted. The basal layer of the epidermis was practically devoid of pigment.

Fig. 3.—Roentgenogram of the feet, showing extensive absorption of bone and also deposits of calcium in the calves.

The more superficial portion of the dermis was vascular, suggesting granulation tissue which had developed into scars. Fairly diffuse mononuclear infiltration occurred, in addition to inconspicuous perivascular cellular infiltration. Hair follicles and sebaceous glands were absent in the sections studied. Rare, indefinite alveoli of sweat glands were noted.

The walls of the arterioles in the deeper part of the dermis or in the more superficial part of the subcutaneous tissue were not especially thick, nor were the arterioles thrombosed. Fairly numerous large vascular spaces in the dermis could

not be identified as dilated veins or lymphatics, because they were empty. No subcutaneous tissue or striated muscle was included in the biopsy specimen.

Stains to demonstrate elastic tissue (Verhoeff's and Weigert's method) revealed absence of elastic fibers in the superficial part of the dermis only (fig. 5). Van Gieson's counterstain showed moderate amounts of collagenous fibers in this part of the dermis. The collagenous fibers were much more delicate than in a control section. Special stains for micro-organisms failed to demonstrate any acid-fast

Fig. 4.—Section of the skin, hematoxylin-eosin stain, showing absence of the rete cones, monocellular infiltration and perivascular involvement. × 100.

organisms. There were a few gram-positive granules, possibly cocci, close to the superficial crust, but nothing resembling pyogenic bacteria deep in the tissue. No structures resembling fungi were seen in any of the sections.

Aerobic and anaerobic cultures of the biopsy material on blood agar and Sabouraud's medium were made, but Staphylococcus aureus-haemolyticus alone was grown. Scrapings from the nasal mucosa were negative for Mycobacterium leprae.

The external cutaneous lesions were treated with compresses of physiologic solution of sodium chloride, but the child complained of burning pain, and the treatment was discontinued. He was given a high caloric diet, which he took

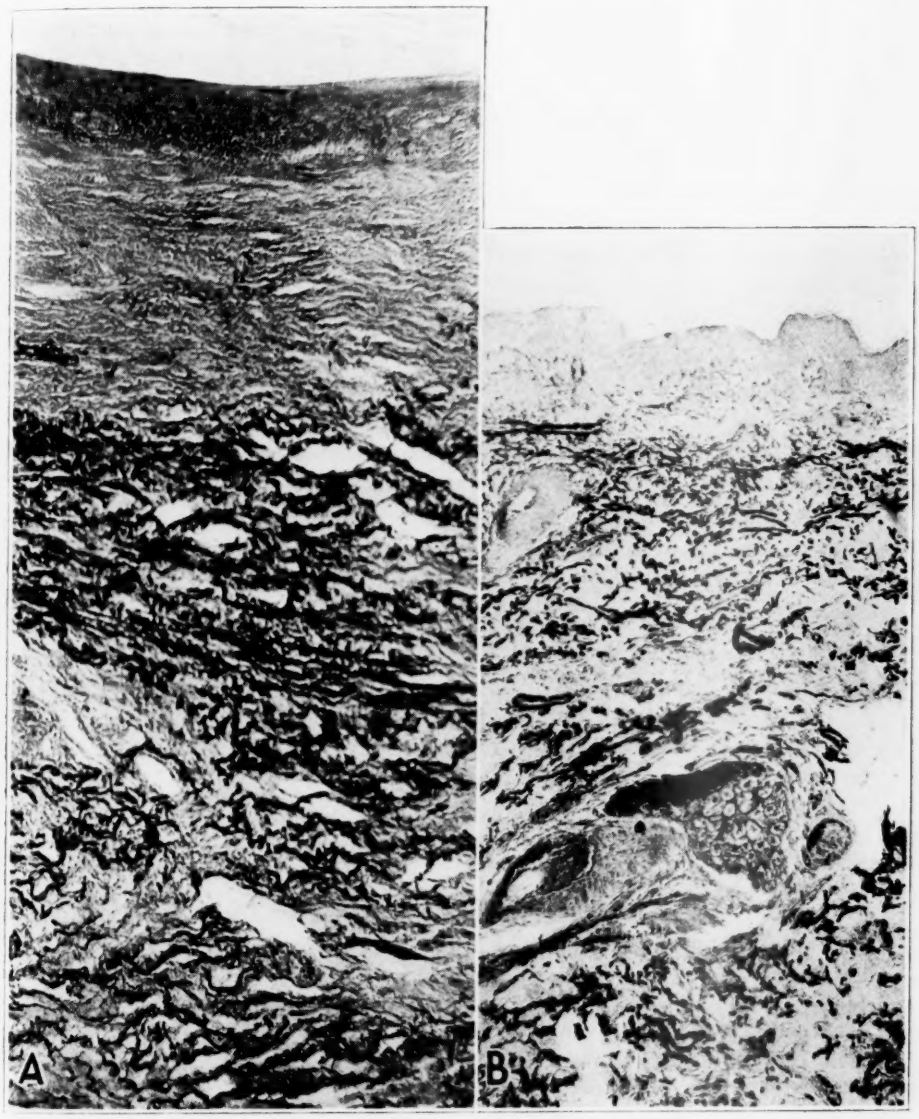

Fig. 5.—*A*, skin treated with Weigert's stain for elastic tissue, showing lack of elastic tissue in the superficial layers. × 100. *B*, normal skin stained with Weigert's stain for elastic tissue. × 100.

well. The food, however, had to be finely divided and pushed down into the pharynx before deglutition could occur. He complained of being too warm, and

an electric fan was used constantly. No specific treatment was attempted. He remained in the hospital for a period of three weeks, during which time no noticeable change in his condition occurred.

The following conditions were suggested as diagnoses:

1. Leprosy: There were no nodules present and no loss of sensation. The phalanges of the hands and the feet were present, the marked nubbing having been due to collapse of the decalcified bones rather than to amputation. The nasal mucosa was very sensitive, and scrapings from this region failed to demonstrate any organisms similar to Mycobacterium leprae. Histologic study of the skin showed nothing suggestive of the disease. Scleroderma-like lesions have been described in leprosy, but in cases of such involvement the lesions usually have been limited to the lower third of the leg; the sclerotic patches have been completely anesthetic, and M. leprae has been found in the involved skin.[3]

2. Epidermolysis bullosa: This is a rare cutaneous disease in which vesicles and bullae are produced by trauma. Two forms have been described, the simple and the dystrophic. In the latter type, bullae appear on the skin following trauma. Crusts then form when the lesion breaks, and over the involved area scarring and pigmentation occur with healing. The extremities often become flexed, owing to atrophic changes in the skin. Dystrophic changes may occur in the nails, resulting in their destruction. This disease usually manifests itself in the neonatal period but may occur within the first two years. It usually runs a chronic course, not responding to any form of treatment.[4]

The condition has been reported in several members of a family. The etiology is obscure. Both congenital absence of elastic tissue and an inflammatory process have been suggested.[5]

The lesions in this disease are usually limited to the extremities and are not as widespread as those in the present case. Stains of the skin for elastic tissue showed this tissue to be present in the deeper layers (fig. 5 *A*). Scales, rather than bullae, seemed to have been the initiating lesions, and these were not preceded by trauma. The child was apparently normal until the age of 2 years, and while epidermolysis bullosa may begin at this age, it usually occurs earlier.

---

3. Denney, O. E.; Hopkins, R., and Johansen, F. A.: Scleroderma-Like Lesions in Lepers, South. M. J. **23**:1003, 1930.

4. Ormsby, O. S.: A Practical Treatise on Diseases of the Skin, Philadelphia, Lea & Febiger, 1927.

5. Engman, M. F., and Mook, W. H.: A Further Contribution to the Study of Elastic Tissue in Epidermolysis Bullosa, J. Cutan. Dis. **28**:276, 1910. Kanoky, J. P., and Sutton, R. L.: Epidermidolysis Bullosa Congenita, J. A. M. A. **54**: 1137 (April 2) 1910.

3. Dermatomyositis: This disease was first described by Steiner as "an acute, subacute or chronic disease of unknown origin characterized generally by a gradual onset with vague and indefinite prodromata, followed by edema, dermatitis and multiple muscle inflammation." [6] The acute stage usually lasts about two months; the subacute, from six to twelve months, and the chronic, from two to three years. The prodromal symptoms, usually general malaise, weakness, fever and vomiting, last about three weeks and are followed by edema, muscular weakness, pain, rigidity and dermatitis. The cutaneous rash in this condition is variable and resembles various types of erythema. Lesions simulating erysipelas, roseola and eczema have been described.[7] Contractures of the joints are not uncommon, and deposits of calcium in the subcutaneous tissues frequently occur. Abnormal amounts of creatine in the urine [8] and of creatinine in the blood [9] have been found. The chronic forms of dermatomyositis have often been confused with the acute type of scleroderma, differentiation being almost impossible since microscopic changes in the skin during these stages are similar.[10]

There is no specific treatment for the disease.[11] Remissions and relapses may occur. Death usually follows the acute forms, but recovery occurs with the subacute and chronic types in about 50 per cent of cases.

The dermatitis in the present case followed a long prodromal period of fever, night sweats, general malaise and anorexia. The cutaneous involvement, however, is not erythematous and is unlike any description of the lesions found in dermatomyositis. Contractures have occurred, as well as deposits of calcium in the remaining subcutaneous tissues. Large amounts of creatine were found in the urine, but this may occur in normal children.[12] This child's disease has been a slowly progressive one, not interrupted by remissions.

4. Pyoderma gangraenosum: The name pyoderma (ecthyma) gangraenosum has been given to a rather rare cutaneous disease associated

---

6. Steiner, W. R.: Dermatomyositis, with Report of a Case, J. Exper. Med. **6**:407, 1904.

7. Stuckey, E. S.: Dermato-Myositis, Brit. J. Dermat. **47**:85, 1935.

8. Ingram, J. T., and Stewart, M. J.: Dermato-Myositis and Poikilodermia, Brit. J. Dermat. **46**:53, 1934.

9. Turner, J. C.: Dermatomyositis, New England J. Med. **216**:158 (Jan. 28) 1937.

10. (*a*) Allan, W.: Dermatomyositis or Scleroderma? Arch. Dermat. & Syph. **19**:265 (Feb.) 1929. (*b*) Brock, W. G.: Dermatomyositis and Diffuse Scleroderma, ibid. **30**:227 (Aug.) 1934.

11. Karelitz, S., and Welt, S. K.: Dermatomyositis, Am. J. Dis. Child. **43**: 1134 (May) 1932.

12. Hunter, A.: Creatine and Creatinine, New York, Longmans, Green & Co., 1928.

with ulceration of the bowels and hypochromic anemia.[13] The lesions that are described usually follow a long, debilitating illness, most frequently ulcerative colitis, but have been reported after empyema, pyelitis and cholecystitis.[14] The initiating cutaneous lesions are discrete small pustules, surrounded by an inflammatory areola, and they usually break down. Healing may occur, but more often an ulcer is formed, which extends to coalesce with other adjoining lesions. The bases of these ulcers are moist and are covered with mucopurulent material. In the acute stages granulation tissue does not occur, but in the chronic stage there is a profusion of this tissue. Healing occurs by epithelial growths from the periphery, with resulting atrophy, scarring and brownish pigmentation of the skin.[13]

From the cutaneous lesions, Staphylococcus albus and Streptococcus haemolyticus have been cultured, and these organisms, when injected into the skin of a guinea-pig, produced similar lesions. The disease is believed to be the cutaneous manifestation of a debilitating disease which clears when improvement in the general condition of the patient occurs.

The cutaneous lesions of pyoderma gangraenosum are not unlike those found in this case. The child suffered from prolonged bloody diarrhea and at present has hypochromic anemia. However, in the cases described in the literature, the cutaneous involvement usually followed an illness lasting from two to nine years. Improvement in these cases also occurred when the underlying infectious process ceased. In my case the diarrhea apparently followed the involvement of the skin, but with its remission, no evidence of improvement in the skin has appeared. On aerobic and anaerobic mediums Staph. aureus-haemolyticus alone was grown from the cutaneous ulcers. However, both staphylococci and streptococci have been cultured from the bacterial flora of ulcers caused by various conditions, and both are considered by some to be secondary invaders.[15]

5. Progressive generalized (diffuse) scleroderma: There are two main types of scleroderma, the circumscribed (morphea) and the diffuse. In the latter a period of fever, anorexia and loss of weight often precedes the actual generalized involvement of the skin. Three stages of edema, induration and atrophy are described, but often the period of edema is short and is not observed. Pigmentation of the skin may accompany the process. In the advanced stages of the disease

13. Brunsting, L. A.; Goeckerman, W. H., and O'Leary, P. A.: Pyoderma (Echthyma) Gangrenosum, Arch. Dermat. & Syph. **22**:655 (Oct.) 1930.

14. (*a*) Lane, C. W., and Strowd, C. M.: Pyodermia Gangrenosum, Arch. Dermat. & Syph. **27**:460 (March) 1933. (*b*) Cohen, M. H.: Pyoderma Gangraenosum: Deficiency Disease Complex, ibid. **33**:813 (May) 1936. (*c*) Brunsting and associates.[13]

15. Engman, M. F., in discussion on Lane and Strowd.[14a] Cohen.[14b]

. . . the entire integument, possibly except the skin of the palms and soles, genitals and perianal regions, and scattered areas on the trunk, presents a waxy-looking smooth, glistening pale or old ivory-yellow, sometimes dirty-brown and mottled, apparently tensely stretched surface. The face is expressionless, mask-like and immobile. The eyelids are fixed and may be ectropic; the eyelashes and eyebrows may be lost. The nose is shrunken, bound down and parrot-like. The ears are shrunken, shiny and seem as though glued to the head. The skin of the neck is stiff and inelastic. The skin covering the articulations is sclerotic and tense, often causing complete ankylosis. In more advanced cases the deeper tissues are implicated, the muscles may undergo shrinkage and atrophy and the bones also may show atrophic changes. The hair and nails become brittle and fall out; the sebaceous and sweat glands are usually diminished.[16]

Ulcers are not uncommon in this disease.[10b] Involvement of the skin of the hands with subsequent atrophic changes in the bones (sclerodactylia) is frequently present in the diffuse form.[17] Deposits of calcium in the subcutaneous tissues and muscles may occur.[18]

The etiology of diffuse scleroderma is obscure.[19] The condition has been attributed to arsenic poisoning,[20] trauma,[21] acute infections,[22] syphilis [23] and neurogenic,[24] toxic,[25] endocrine [26] and vasomotor [27] disorders.

16. Wise, F.: Scleroderma, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1927, vol. 3, p. 333.

17. Edeiken, L.: Scleroderma with Sclerodactylia: Report of Three Cases with Roentgen Findings, Am. J. Roentgenol. **22**:42, 1929. O'Leary, P. H., and Normland, R.: A Clinical Study of One Hundred and Three Cases of Scleroderma, Am. J. M. Sc. **180**:95, 1930. Pletnev, D., and Plotkin, T.: Sclérodermie avec sclérodactylie traitée par la sympathectomie cervicale, Presse méd. **43**:1653 (Oct. 23) 1935.

18. Durham, R. H.: Scleroderma and Calcinosis, Arch. Int. Med. **42**:467 (Oct.) 1928. Scholz, Thomas: Calcification in Scleroderma with Report of a New Case, Am. J. Roentgenol. **28**:92, 1932. Durham, R. H.: A Case of Scleroderma with Extensive Subcutaneous, Periarticular and Vascular Calcification, Ann. Clin. Med. **5**:679, 1927. Thibierge, G., and Weissenbach, R. J.: Concretions calcaires sous-cutanées et sclérodermie, Ann. de dermat. et syph. **2**:129, 1911. Brody, Joseph, and Bellin, David E.: Calcinosis with Scleroderma, Arch. Dermat. & Syph. **36**:85 (July) 1937.

19. Boardman, W. P.: Scleroderma, with Special Reference to Its Etiology and Treatment, Arch. Dermat. & Syph. **19**:901 (June) 1929.

20. (*a*) Moench, L. M.: Chronic Arsenic Poisoning in a Child Associated with Profound Anemia and Scleroderma, New York State J. Med. **36**:1029 (July 15) 1936. (*b*) Ayres, S., Jr.: Scleroderma as a Possible Manifestation of Chronic Arsenic Poisoning, Arch. Dermat. & Syph. **2**:747 (Dec.) 1920.

21. Dercum, F. X.: A Case of Scleroderma of Traumatic Origin, J. Nerv. & Ment. Dis. **21**:198, 1894.

22. MacKenzie: Scleroderma: Report of a Case, Brit. J. Dermat. **19**:404, 1907. MacCollum, W. G.: Acute Diffuse Scleroderma, Tr. A. Am. Physicians **41**:190, 1926.

23. Murray, W. E.: Scleroderma and Syphilis, Brit. J. Dermat. **39**:201, 1927.

24. Sequeira, J. H.: Two Cases of Frontal-Nasal Morphoea with Remarks, Brit. J. Dermat. **23**:40, 1911.

(Footnotes continued on next page)

There are no constant pathologic changes in the skin or in other parts of the body. The ultimate changes in the skin and the muscles may be due to a nonspecific capillary endarteritis, preceded by edema and cellular infiltration and followed by degeneration, fibrosis and atrophy. Similar changes have been found in dermatomyositis and in other cutaneous conditions in which atrophy or scarring occurs.[28]

The biopsy apparently aided little, except in demonstrating the presence of chronic dermatitis. The changes described were those which

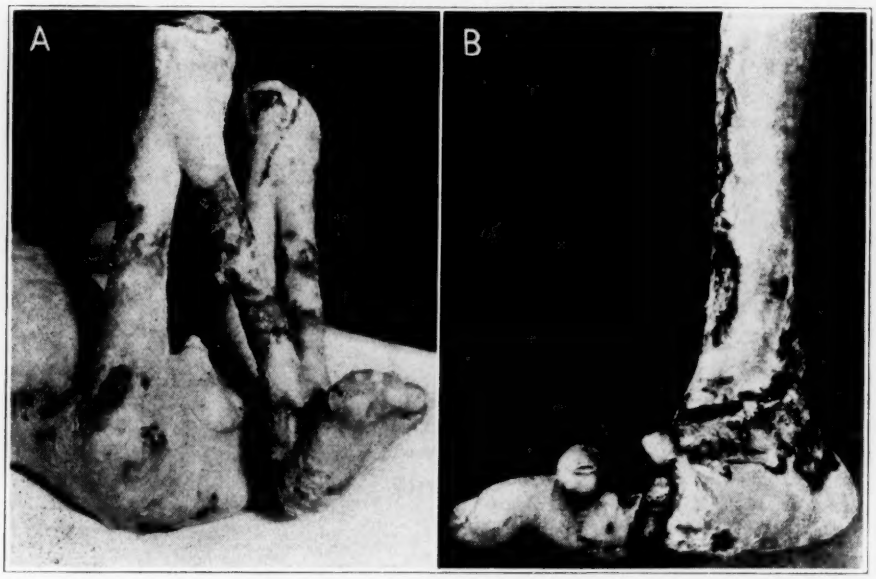

Fig. 6.—*A*, lower extremities of the patient in the case reported. *B*, lower extremity of the patient in Williams' case.

---

25. Cornbleet, T., and Struck, H. C.: Calcium Metabolism in Scleroderma, Arch. Dermat. & Syph. **35**:188 (Jan.) 1937.

26. Castle, W. F.: The Endocrine Causation of Scleroderma, Including Morphoea, Brit. J. Dermat. **35**:254, 1923. Little, E. G. G.: Case of Scleroderma Associated with Graves' Disease and Later Myxedema, ibid. **28**:124, 1916. Seale, E. R.: Endocrine Aspects of Scleroderma: Report of a Case with Glandular Dysfunction, South. M. J. **22**:885, 1929. Sequeira, J. H.: Case of Sclerodermia (Sclerodactyly Type), with Adrenal Insufficiency, Brit. J. Dermat. **34**:124, 1922. Selye, H.: Die Sklerodermie und ihre Entstehungsweise, Virchows Arch. f. path. Anat. **286**:91, 1932. Longcope, W. T.: Hypoglycemia in Scleroderma, J. A. M. A. **90**:1 (Jan. 7) 1928.

27. Brown, G. E.; O'Leary, P. A., and Adson, A. W.: Diagnostic and Physiological Studies in Certain Forms of Scleroderma, Ann. Int. Med. **4**:531, 1930.

28. Longmead, F. S.: Relationship Between Certain Rare Diseases: Generalized Scleroderma, Calcinosis, Dermatomyositis, Myositis, Fibrosis, Arch. Pediat. **40**:112, 1923. Allan.[10a] Brock.[10b]

would be expected with chronic inflammation adjacent to cutaneous ulcerations. Hence, no conclusions could be drawn as to the nature of the underlying dermatologic disease if one was present. It is doubtful that a biopsy specimen could have been selected from any portion of the cutaneous surface where changes secondary to ulcerations might not have occurred. Biopsy of muscle might have added some information.

Diffuse scleroderma appears to be the most likely diagnosis. A prodromal period of fever, malaise, anorexia and loss of weight occurred and was followed by involvement of the skin, with subsequent contractures, deposition of calcium and atrophic changes. Extensive osseous atrophy and absorption have occurred throughout the long bones, being especially marked in the phalanges of the hands. No stage of edema was noted, but it may have been present during a short period without being detected. The disease is rare before puberty; its occurrence at earlier ages, however, has been reported.[29] Williams has reported an unusual case of diffuse scleroderma in a 7 year old child whose cutaneous lesions and muscular and bony changes, while not as extensive as those found in this case, were identical with them (fig. 6).[30]

COMMENT

There is no specific treatment for diffuse scleroderma. Improvement has been reported to follow intravenous injection of sodium thiosulfate (in arsenic poisoning)[20a] or hypertonic salt solution,[31] parathyroidectomy,[32] sympathetic ganglionectomy,[33] administration of arsenic

29. (*a*) Oliver, F. L.: Generalized Scleroderma in Children, Arch. Dermat. & Syph. **25**:72 (Jan.) 1932. (*b*) Seifert, A.: Sklerödem bei einem 6 Jahre alten Kinde, Arch. f. Kinderh. **91**:220, 1930. (*c*) McCrackin, R. H.: Scleroderma: Report of a Case with Sclerodactylia and Hemiatrophy, J. Pediat. **9**:173, 1936. (*d*) Cohen, P.: Scleroderma and Sclerodactylia in a Child, Am. J. Dis. Child. **46**:214 (July) 1933.

30. Williams, C. M.: A Case of Diffuse Scleroderma Presenting Unusual Features, Arch. Dermat. & Syph. **9**:187 (Feb.) 1924.

31. Herzog, F.: Treatment of Scleroderma by Intravenous Injection of Sodium Chloride Solution, Med. Klin. **22**:1178 (July 30) 1926; abstr., J. A. M. A. **87**:1344 (Oct. 16) 1926.

32. Garlock, J. H.: Parathyroidectomy for Raynaud's Disease and Scleroderma, S. Clin. North America **16**:771, 1936. Ramsdell, E. G.: Calcinosis Universalis, West. J. Surg. **43**:624, 1935. Leriche, R.; Jung, A., and De Bakey, M. E.: The Surgical Treatment of Scleroderma: Rationale of Sympathectomy and Parathyroidectomy, Based upon Experimental Investigations and Clinical Study of Twenty-Six Personal Cases, Surgery **1**:6, 1937.

33. Craig, W. M., and Kernohan, J. W.: The Surgical Removal and Histological Studies of Sympathetic Ganglia in Raynaud's Disease, Thrombo-Angiitis Obliterans, Chronic Infectious Arthritis, and Scleroderma, Surg., Gynec. & Obst. **56**:767, 1933. Brown, G. E.; O'Leary, P. A., and Adson, A. W.: Surgical Treatment of Vasospastic Type of Scleroderma by Resection of Sympathetic Ganglia and Trunks, Ann. Int. Med. **4**:555, 1930.

(in syphilis),[19] insulin,[34] desiccated adrenal gland,[35] thyroid,[36] ovary,[37] pancreatin,[38] posterior pituitary,[39] radium[40] or preparations of vitamin D[25] or of thorium[41] or the use of a ketogenic diet.[42]

The disease usually runs a chronic course, death resulting from a superimposed intercurrent infection. The prognosis in children is considered to be better than that in adults, and spontaneous recovery often occurs when the deeper structures are not involved.[29e]

SUMMARY

An unusual case is reported.

In the differential diagnosis leprosy, the dystrophic form of epidermolysis bullosa, dermatomyositis, pyoderma gangraenosum and progressive generalized scleroderma are considered.

This case is believed to be one of progressive generalized scleroderma with sclerodactylia and calcinosis.

Drs. A. H. Elliott and W. D. Carter, of Wilmington, N. C., assisted in securing the hospitalization of the patient.

34. Wahl, E. F.: Scleroderma: Insulin Therapy, J. M. A. Georgia **19**:285, 1930.

35. Winfield, J.: A Case of Scleroderma Improved Under the Use of Dessicated Suprarenal Gland, J. Cutan. Dis. **22**:587, 1904.

36. Robinson, A. S.: Report of a Case of Scleroderma of the Skin, Am. J. M. Sc. **54**:657, 1917.

37. Jeanselme, E., and Burnier, R.: Sclérodermie en plaques avec dyschromie pigmentaire symétrique, Bull. Soc. franç. de dermat. et syph. **33**:704, 1926.

38. Sellei, J.: Die Akrosklerosis (Sklerodaktylie) und deren Symptomenkomplex nebst neueren Untersuchungen bei Sklerodermie, Arch. f. Dermat. u. Syph. **163**:343, 1931.

39. Oliver, E. L., and Lerman, J.: Scleroderma Treated with Injections of Posterior Pituitary Extract, Arch. Dermat. & Syph. **34**:469 (Sept.) 1936.

40. MacKay, H.: Scleroderma and Its Treatment by Radium, Canad. M. A. J. **16**:142, 1926.

41. Epstein, S.: Zur Behandlung von Sklerodermie und Acrodermatitis chronica atrophicans mit Thorium X (Degea), Arch. f. Dermat. u. Syph. **167**: 533, 1933.

42. Kennedy, R. L. J.: Calcinosis and Scleroderma: Treatment of a Case by Use of the Ketogenic Diet, J. Pediat. **1**:667, 1932.

Progress in Pediatrics

OBJECTIVE RATINGS OF THE CONSTITUTION OF THE GROWING CHILD

BASED ON EXAMINATION OF PHYSICAL DEVELOPMENT AND MENTAL EXPANSION

T. WINGATE TODD, F.R.C.S. (LONDON)
CLEVELAND

In a recent address Lord Horder [1] spoke of the reference of the physician, including in this quaint but vivid phrase three duties, namely, to heal the sick, to prevent disease and to gain control of the biologic principles of life in the interest of the public. As physicians, we have been trained to heal the sick as our first duty. Preventive medicine has impressed on us our responsibility in safeguarding the public against the scourge of disease. But in my function as an anatomist engaged in the study of growth and repair, it is toward the control of the biologic principles of life that I wish to direct your attention in this lecture. Macpherson Lawrie [2] has pointed out in his recent book that the real tragedy of illness is not the illness of the hospital and the institution, not the illness which the doctor sees, but the illness which cripples healthy living, haunts the worker and pervades the home. We are then addressing ourselves to the assay of subclinical handicaps which do not drive their victims across the threshold of the doctor's office, bearing in their bodies the ravages of established disease or in their brains the terminal symptoms of a disordered mind.

Now I could wish no greater privilege than the opportunity of discussing this theme as it affects ourselves, for how many of us, having passed the age of 50, can honestly claim to have realized in our experience the hopes, the ambitions or even the domestic happiness which we expected? But I voluntarily limited myself in my title to the growing child. This was natural, for two reasons. First, biologically speaking, whatever we may do for the adult is but repair work for today, but

From the Western Reserve University School of Medicine.

The Lewis Linn McArthur Lecture, delivered before the Institute of Medicine, Chicago, Feb. 26, 1937.

1. Horder, Thomas Jeeves: Euthanasia: The Reference of the Physician, Manchester Guard. Weekly **34**:446, 1936.
2. Lawrie, M.: Nature Hits Back, London, Methuen & Co., Ltd., 1936, pp. 2 and 89.

in our constructive work for children we are imaginatively building the nation of tomorrow. Secondly, my professional life has been largely spent among children and students—children because of my training as a pediatrician under Ashby and my directorship of the Developmental Health Inquiry in Cleveland, and students because of my vocation as a practicing anatomist, first in Manchester and then in Cleveland, these thirty years. The passage of these years has fixed in me the conviction that it is not the fully established and spectacular breakdown that destroys the happiness of living and warps a nation, but those early, unrecognized and widely spread subclinical handicaps which cripple confidence, initiative and efficiency, impair daily achievement and satisfaction, shatter ambition and cast a gray veil of uneasiness over what should be the very joy of life.

The study of the growing child is, moreover, less subtle than that of the adult. His daily words, his satisfactions, repressions, apprehensions, ambitions and dejections are written large and plain for all to see, not hidden away by long-established habit. His thoughts are obviously as fidgety as his muscles. His life is one of progress, the attainment of well defined and registrable stages, lending itself to analysis of the date and origin of deficiencies with a precision denied us in the investigation of adult adjustment. Out of the mass of data accumulated during the systematic, longitudinal study of the apparently healthy and well circumstanced children of Cleveland in the Developmental Health Inquiry, I have selected some definite ratings which bear on the appraisement of constitution.

HEIGHT AND WEIGHT

First, let us consider height and weight, not in the light of their absolute values, which may not mean much, but from the point of view of steadiness of increment. Low absolute values for height and weight may mean not a lagging increment but a defect of growth occurring at a much earlier age and never thereafter compensated by increased velocity of increment. During the aforementioned survey, our statistician, Miss Simmons, made a series of individual curves of growth based on the longitudinal study of approximately one hundred boys and one hundred girls. Each child was examined serially, without intermission due to illness, from the age of 3 months to that of 7 years. The older siblings of these children permitted continuance of the growth curve to the age of puberty. The striking fact about these curves is the almost undeviating steadiness of increment in growth characteristic of health and of evenly progressing physical maturation. Once the curves have stabilized their slope, at about the age of 2 years, the increment approximates 55 mm. and 5 pounds (2 Kg.) a year during the asexual

period (see also Gray and Ayres,[3] Meredith [4] and Scammon [5]). When the tenth birthday is passed the composite curve for increment in stature rises with no greater steepness for girls until the thirteenth birthday or for boys until the fifteenth, after which it falls off for both sexes, to fade out in the later teens. The fact that there is no increased steepness of the composite curve for stature during preadolescence means not that children themselves cannot show increased velocity of growth but only that for those in whom there is first a diminished and then an increased velocity the modifications occur at different ages in different children, according to progress in physical maturity. This smooths out a composite curve. From the ninth to the thirteenth birthday for girls and from the tenth to the sixteenth for boys the weight curve shows enhanced increment, rising to a maximum of about 10 pounds (4.5 Kg.); but again the striking feature of the gain is its steadiness.

The analysis of increment in height and weight of any child calls for information on four points: (1) his progressive physical maturity, (2) identification of the segments of the body in which the increment of height is evident, (3) his health history and (4) his family line. But let us leave these features of analysis for later consideration and discuss only the attainment of satisfactory progress year by year. It does not matter greatly from what base line the increment is computed provided a satisfactory gain is attained for the time elapsed. Precautions must of course be taken. Stature must be measured as horizontal length, not as standing height, which is affected by posture. Accuracy in weighing must be safeguarded by removal of shoes and superfluous clothing. Measurements of both height and weight must be made at approximately the same date in successive years. This does not mean that measurements should not be made more frequently. But determinations of stature do not lend themselves to measurements at intervals of less than six months, especially when young children are concerned, for, as Scammon has pointed out,[5a] an error in determination is shown by Lincoln's [6] figures to be the equivalent of six months' growth. Weight, however, is much more sensitive, and systematic determinations of weight give valuable information on constitutional progress. Allergic children may regularly fail to gain properly in weight during the active

3. Gray, H., and Ayres, J. G.: Growth in Private School Children, Chicago, University of Chicago Press, 1931.

4. Meredith, H. V.: The Reliability of Anthropometric Measurements Taken on Eight and Nine Year-Old White Males, Child Development **7**:263-272, 1936.

5. Scammon, R. E.: Recent Work on the Physical Development of Children, Proc. Conf. Research in Child Development, 1927, pp. 8-15.

5a. Scammon (footnote 5 and personal statement).

6. Lincoln, E. A.: The Reliability of Anthropometric Measurements, Pedagog. Semin. & J. Genet. Psychol. **38**:445-450, 1930.

phase of the handicap and may partly or fully make up for this during the period of the year when the allergy is masked. As the active phase may occur in winter, in summer, in the fall or in the spring, the child should be weighed regularly every three months and the gain carefully studied. Alternating gain in weight by season through the year may cause the physician and parents to suspect that the child is suffering from a subclinical handicap of which there are no overt symptoms.

In the curve for increment in stature are two critical points. The first occurs at the change from the asexual phase of childhood to the sex-dominated phase in preadolescence. I shall come to that in a moment. The second occurs at about the thirteenth birthday in girls and the fifteenth in boys. In turning to the roentgenograms of children whose increment of stature illustrates this statement, one finds that the epiphyses at the knee permit no more growth after these birthdays. The epiphysis for the lower end of the tibia has already united and at the upper end of the femur there is relatively little growth, so that, with imminent union of the epiphyses at the knee (lower femur, upper tibia), growth in the leg practically comes to an end. Further growth in stature must therefore occur in the trunk (vertebral column). This accounts for the rapid decrease of increment in growth beyond these critical birthdays.

With this division of increment in stature into the components for the leg and the trunk, let us recall that in 1893 Boas and Woodbury measured the increments in stature and West [7] the sitting height in children of Worcester, Mass. If one makes a composite curve of increment which combines the sitting height of the Worcester children and the leg length of the Cleveland children in our study, one derives the curve for increment in stature shown in the Worcester figures. But our increments in leg length show a steady, uniform gain year by year in childhood, preadolescence and adolescence till the birthdays already mentioned. Any increased increment in stature evident in the preadolescent phase lies in the trunk, not in the leg. The inception of this increased increment in trunk length marks the onset of the sex-dominated phase of child growth.

This sex-dominated increment in trunk growth can be indirectly inferred by another method of approach. Transverse lines or scars on the bones result from any temporary interference with growth due to illness, injury or surgical intervention. These remain for a varying length of time and then disappear. So long as they remain, they provide a basis from which to measure the increment of growth in the particular bone in which they occur. A study of these scars was under-

7. West, G. M.: Anthropometrische Untersuchungen über die Schulkinder in Worcester, Mass., Amerika, Arch. f. Anthropol. **22**:13-48, 1893.

taken by Seymour and me [8] to determine the yearly growth in the tibia, the femur and the torso. In early childhood the proportion of leg growth to trunk growth is about 4:3. This proportion is retained until approximately the eleventh birthday, when it fails, owing to increased velocity of trunk growth.

Roentgenograms, however, are not necessary for this analysis. Taking the height of the iliac crest from the ground is an efficient method of measuring increment in leg length.

Failure of the child to conform to this pattern of growth is usually the earliest indicator of a future metabolic variant in attainment of the sex-dominated phase of childhood. Children in whom we have later identified delayed adolescence have already shown in the asexual phase increments of leg growth and trunk growth in the proportion of 2:1, or even 3:1. If one waits to institute corrective measures of endocrine imbalance until the roentgenogram of the hand shows delayed progress in maturity when puberty should approach, or if one waits until failure of growth in the trunk makes itself obvious, the opportune moment will have been missed and corrective measures will fail. Treatment for endocrine imbalance, to be successful, must begin before the close of the asexual phase in childhood.

Several years ago Boas,[9] using increased velocity of increment in stature characteristic of preadolescent life as his guide, showed statistically that boys fall into two groups, one of which matures early and the other late, there being about two years' difference between the groups. This divergence is evident in our series also, though, rather than distinction into two definite groups, there is a range of about two years during which increased velocity of increment in stature may commence. This is characteristic also of girls. It represents empirically the extent of divergence which may be allowed within the range of the nonpathologic. This is an obscure phrase: It is obvious that the problem of divergencies in growth pattern can be satisfactorily explained only on the basis of additional facts which should now be considered.

BODILY MATURATION

From the point of view just presented, growth in dimensions becomes a correlate, if not a sequence, of progressive physical maturity which expresses itself in the bodily framework. Many years ago Keith divided growth into functional and corporeal concomitants. But he was

8. Todd, T. W., and Seymour, W. B.: The Growth of Long Bones, to be published.

9. Boas, Franz: Analysis of the Growth Curve of Man, Science **71**:545-546, 1930; Observations on the Growth of Children, ibid. **72**:44-48, 1930; Studies in Growth, Human Biol. **4**:307-350, 1932; **5**:429-444, 1933; **7**:303-318, 1935.

speaking of organs, not of the bodily frame. In its development an organ must reach a certain size before it is functionally efficient; thereafter, it may grow in size in response to bodily requirement, but its functional efficiency is unaffected. The lung, for example, is structurally fully mature at birth, though it still has considerable growth to undergo before it reaches adult size. The bodily frame is not structurally mature until the third decade of life. Evidence of this progressive maturation presents itself in all the supporting tissues, but is most readily measured in the skeleton by the changes taking place at the growing ends of bones and in the epiphyses. Considerable effort has been devoted by many observers to establishing means of measuring this progressive maturity. These have failed to be convincing because the distinction between growth and maturation has not been fully appreciated. For infants and young children, determinations have been based on the date of ossification of the secondary centers or on the spread of ossification in the cartilages in which these secondary centers occur. This approach could not be successful because it seeks to define maturation in terms of dimension, a method which has been seen to fail even if applied to the bodily framework as a whole. There is, however, one feature of progressive maturation in the skeleton which has impressed itself on the attention, namely, the fusion of an epiphysis with the shaft of a bone. If, then, attention is devoted to the changes in the epiphysis which culminate in this fusion, there will be better hope of success. The epiphyses of the knee will serve as an example. A series of roentgenograms of the knee taken, say, at the ages of 3, 6, 9, 12 and 15 years, shows progressive stages in the ossification of the epiphyses. These stages are expressed, not in the mere increase in size of the bony nodule, but in the change in contour of the nodule, terminating in complete ossification of the epiphysial cartilage and followed by obliteration of the diaphyso-epiphysial plane. In the several mammalian orders there are great divergencies in the relative length of time which elapses between complete ossification of the epiphysis and its fusion. In rodents fusion is delayed, but in primates it occurs relatively soon after completion of epiphysial ossification. This juxtaposition in time has misled previous observers into the assumption that growth is necessarily continuous until union of the epiphysis finally precludes its occurrence. Even in man normal growth in the shaft of the major long bones ceases about nine months before the epiphysis unites.

Ten years' intensive study of the stages of maturation in epiphysial ossification has enabled us to draw up a sequence of characteristic features which serves as a yardstick by which to measure progress. Determinations of progress can be made at the knee, elbow, hip, shoulder, foot or hand. Of these, the hand is the most generally serviceable. Although the general principles on which the maturation yardstick is

constructed were published several years ago,[10] the final atlas was completed only recently.[11]

Just as growth must be divorced from maturation in our thought, so must time. Or rather, physiologic time must be differentiated from chronologic time. One child at 12 years of age may show the phase of maturation which is evident in another child at 14 years and in a third at 10 years. In other words, observations on maturation must be expressed in terms of progress, just as observations on growth must be stated in terms of increment. In preadolescence metabolic energy is directed more toward increment in growth than toward progress in maturation. In adolescence the emphasis is reversed: Increment in growth is slowed, while progress in maturation is accelerated. Owing to the fact that in the primate skeleton union of epiphyses follows relatively rapidly on completion of epiphysial ossification, observers have been prone to assume that growth at the end of a particular shaft ceases because union of the epiphysis alone stops it. It is true, of course, that so long as an epiphysis remains unfused growth in the adjacent end of the shaft is possible; but this does not imply that growth will take place after, or even can be induced by, therapeutic treatment. Thus, the Lorain type of dwarf, whose epiphyses are not fused, still may not grow.

Boas' two types of growth in preadolescence are then explained on the basis of early and late adolescence. They represent the range which may be expected in the attainment of a certain stage in the progress of bodily maturation, a stage which can easily be identified in roentgenograms of the knee, and, with the knee as criterion, in roentgenograms of other parts of the body, such as the hand.

SKELETAL MATURATION AND THE MENARCHE

Further evidence that progress in skeletal maturation is a reliable indicator of progress in bodily maturity is given by our observation that the menarche occurs in girls at a time when the skeletal roentgenograms register a maturity level between the arbitrarily numbered stages 29 and 30. This level for the girls in our series is usually reached approximately at the age of 13 years and 6 months, but may not be attained until two years later by girls of delayed adolescence.[12] While

10. Todd, T. W.: Growth and Development of the Child: Roentgenographic Appraisement of Developmental Growth in the Skeleton: IV. Appraisement of the Child, in White House Conference on Child Health and Protection, New York, D. Appleton-Century Company, Inc., 1932, pt. 4, pp. 258-279.

11. Todd, T. W., and others: Atlas of Skeletal Maturation: I. Hand, St. Louis, C. V. Mosly Company, 1937.

12. Pearl, R.: Biological Factors in Fertility, Ann. Am. Acad. Polit. & Soc. Sc. **188**:14-25, 1936; table V, p. 20.

the great majority of girls conform to this relationship, there are exceptions. Hence it must be inferred not that there is a direct correlation but rather that both skeletal and gonadal maturation are dominated by some common factor.

Attempts have been made to determine a corresponding stage of gonadal maturation in boys by utilization of the appearance of pubic hair (Crampton[13]), examination of morning urine (Baldwin[14]) or measurement of genitalia (Davenport[15]). None of these methods is really practicable. But since boys at the age of 15 years and 9 months reach our roentgenographic stage 34, corresponding on the average to the level attained by girls at the age of 13 years and 6 months,[11] we may infer that gonadal maturation follows approximately the same course.

ROENTGENOGRAPHIC EVIDENCE IN TEXTURE OF BONES

So far, the criteria of constitutional health which have been noted are those of progress in physical growth or maturity. There are, however, other criteria of soundness of constitution which can be elicited from the roentgenogram. These are, respectively, scorings and mineral density.

Scorings on Bones.—Scars or transverse lines on the bones[16] have been noted after illness, injury or surgical intervention, the bones being most susceptible to these at about the age of 4 years.[8] There are, however, lighter markings, resembling watered silk, which make their appearance on the shaft near the growing end, more frequently at the lower end of the tibia, at the lower end of the radius or, more rarely, at the knee. These result also from temporary interruption of growth, more fleeting, however, than the interruptions which result in scars. We have seen these scorings most frequently in children showing overt evidence of gastro-intestinal sensitivity, but they occur also in children in whom skin tests reveal no indication of susceptibility to food allergens. We regard these scorings as evidence of gastro-intestinal irritation and look on them as indicators more sensitive than skin tests for food allergy. The presence of these scorings is warning that other subclinical evidence of allergy should be sought in mild digestive disturbance, con-

13. Crampton, C. Ward: Physiological Age: A Fundamental Principle, Am. Phys. Educat. Rev. **13**:141-154, 214-227, 268-283 and 345-358, 1908.

14. Baldwin, B. T.: The Determination of Sex Maturation in Boys by a Laboratory Method, J. Comp. Psychol. **8**:39-43, 1928.

15. Davenport, C. B.: Adolescent Spurt in Growth, in Memorial volume in honor of the 60th birthday of Prof. Dr. V. Růžička, Prague, 1930.

16. Park, E. A., and Howland, J.: The Radiographic Evidence of the Influence of Cod Liver Oil in Rickets, Bull. Johns Hopkins Hosp. **32**:341-344, 1921.

gested turbinates or hazy antrums. Scorings are often precursors of allergic symptoms which will appear when the constitutional handicap reaches an overt stage.

Mineralization.—The roentgenographic shadow of a bone should show a dense, well defined substantia compacta with a substantia spongiosa in which the trabeculae, especially at the metaphysis near the growing end, are partially obscured by a gray film of labile mineral, forming the store from which the mineral of the blood is replenished. When the demands for mineral are great in consequence of rapid growth, as in infancy and preadolescence, this labile store may be temporarily diminished, resulting in clearer tracery of trabeculae. Children of impoverished constitution, whether from prolonged toxemia, protracted ill health or inability to utilize mineral, show more pronounced reduction of the labile mineral, with encroachments even on the trabeculae themselves, which become thin or fragmented. The mere feeding of mineral by mouth to these children, or even the intravenous administration of mineral, may not produce any replenishment of the labile mineral in the substantia spongiosa. Such children are the despair of the orthodontist, who relies on the metabolic integrity of the osseous tissue in the jaws to second his efforts at realinement of teeth.

We find that disturbance of mineralization is more prevalent in girls in the second decade of life than in boys, and in women than in men.

THE HIGHLY STRUNG CHILD

Further exploration is necessary to define clearly the full clinical significance of variants in the mineral store of bones. So frequently do we find lightly mineralized bones in the highly strung child, who is prone to fatigue, restless, often very alert, irritable, poorly adjusted, apprehensive and fearful, with deficient powers of attention and concentration, that we have come to suspect deficiency in mineralization as the physical counterpart of this emotional maladjustment. But one should point out that one is dealing here not with cause and effect but merely with different aspects of a constitutional handicap. Fatigue, apprehension and lethargy are the chief subclinical deterrents from constitutional fitness, but they rarely come to the notice of the physician in their early stages, when correction might be a relatively simple problem.

At 18 months of age, for example, when apprehensiveness is most frequent and most vigorously expressed, it is rationalized by many parents, physicians and psychologists as a stage in adjustment which is precipitated by inadequacy of communication between the child and those responsible for his welfare. It is true that a minority of children of this age are socially well adjusted, but our objective experience dem-

onstrates that children belonging to this minority are likely to be well grown and skeletally well matured for their age, with bones showing good mineralization and free from scorings.

THE CLOUDED INTELLIGENCE QUOTIENT

In childhood and adolescence proneness to fatigue, apprehension and lethargy damp zest, lower efficiency, promote morbid moods, enhance solitariness, shatter ambition and produce domestic unhappiness. The child's scholastic record falls off, and a vicious cycle is instituted, which may send him ultimately to a psychiatrist or to the child guidance clinic. But a careful study of his subclinical handicaps, reenforced by an investigation of his constitution by the simple means suggested in the foregoing part of this address, may well define the lines of successful management and restore the child's life to that vivid reality which is his birthright. Liss [17] has pointed out that the well adjusted child is the child whose school attendance is good (personal statement). He is free from the constitutional deterrents which I have emphasized, namely, in proneness to fatigue, apprehensions and lethargy. I am, of course, speaking not of the child whose metabolic balance is so far off center that he is in urgent need of immediate medical aid but merely of the child whose school records or psychologic tests register achievement rather than capacity. "Education," as Lawrie pointed out, "deals with organic substances. When education fails, it fails not so much because the child lacks mental capacity as because of some constitutional handicap resulting in a strength, possibly of the highest merit, which refuses to accept coercion, or a weakness which impairs, beyond the limit of compensation, his achievement of the standard which is his true métier." [2]

PHYSICAL DISHARMONY IN THE CHILD

Frequently, in roentgenographic assessments of physical maturity in children, difficulty arises from the conflicting levels of maturity shown in different areas of the skeleton. This is an indication of constitutional instability. If the defect is more pronounced, physical maturation is out of harmony with the other features of physical growth, of age or of intellectual attainment. The child, for example, whose physical development is retarded lacks that biologic slate on which the experience of his years should be registered. He acts and looks immature for his age. His outlook, in other words, is younger than his years.

If, however, his physical maturity is beyond his age, he is apt to stumble because his experience, being inadequate for his inner urge,

17. Liss, E.: Emotional Development of the Child from Eight to Fifteen, in Growth and Development, the Basis for Educational Programs, New York, Progressive Education Association, 1936, pp. 73-75.

fails to invoke that balanced judgment which is essential to good adjustment. It is significant that the majority of the girls whom we have examined for the Girls' Bureau, girls who have been referred to that agency on account of some domestic infelicity, show a mental age not exceeding 13 years but a physical development from two to four years in advance of their chronologic age. Their aspirations, ambitions and yearnings are out of harmony with their age and experience and provoke coercion or repression by sorely tried or unsympathetic parents.

What do we look for in the children of the future? "A body," as Cyril Norwood has said, "that can be trusted to do what the will commands"; [18] a mind alert and responsive, which acts with decision; a spirit quick to sense its social obligations and hold the balance between impulse and restraint; stature within reasonable limits; weight that means energy and not encumbrance; physical development to match experience and experience to match years; flexibility of imagination; well disciplined thought; good power of attention and concentration; the ability to discern broad connections; fertility in resource; catholicity in cultural application; artistic capacity; instinctive grasp of timeliness and propriety; intellectual and social adjustment to the ways of others and an unerring sense of responsibility to the ideal which beckons ahead.

I shall not pursue this theme which I have sketched in broad outline, simply to bring it to your attention, with its hopeful possibilities for the future. I close with an expression of faith in the children of the future whose lives shall be transformed from dull existence to vivid actuality through the ministration and education which can be secured by a medical profession quick to perceive the earliest signs of disability before they reach that stage when illness, humiliation or apathy has brought them to our office door.

---

18. Norwood, C.: Address at the British Association, Manchester Guard. Weekly **31**:213, 1934.

Correspondence

ABSORPTION OF INGESTED CALCIUM IN RACHITIC RABBITS

To the Editor:—In a paper previously published in this journal (Hamilton, B., and Schwartz, C.: Rickets and Hyperparathyroidism, Am. J. Dis. Child. **46**:775 [Oct.] 1933), experiments were reported in which the administration of a soluble calcium salt by stomach tube to rachitic rabbits was followed in most cases by an immediate and marked rise of the serum calcium, while normal controls, of the same age as the rachitic animals, and given the same dose of calcium, showed a much more moderate rise of the serum calcium.

In a personal communication, Dr. Richard H. McCoy has informed me of the results of experiments in which he failed to confirm the observations just cited. The experiments were then repeated by us, and it was found that in this new series of rachitic animals the marked rise in serum calcium previously obtained was not observed. As shown by Dr. McCoy, however, the previous results can be duplicated if the tube is introduced, not into the stomach, but into the trachea of the animal. If that is done, marked rises of serum calcium are obtained both in rachitic and in normal animals.

In order that one may explain our earlier results, this possibility (the introduction of the tube into the trachea) must be taken into consideration. It seems rather unlikely, however, that this accident could have happened in twenty-six of thirty-three rachitic animals without occurring in any of the sixteen controls, unless one assumes that, owing to some condition peculiar to rickets, the stomach tube could more easily enter the trachea in the rachitic animals. This, however, does not seem to be the case, because if the animals are kept in the sitting position (as they were in our first experiments) it is difficult even intentionally to introduce the tube into the trachea of a rachitic animal.

There might, of course, have been other accidents or errors of technic, the discussion of which would hardly be of interest; or the technic may have been faultless but some factor the importance of which we did not recognize may have been present in our previous experiments. Since, however, we have not been able to find any such factor, we feel that the present communication is indicated.

The paper in which these data were published also contained a report of other experiments, which concerned the presence of abnormally high amounts of parathyroid hormone in the blood of rachitic animals. Our failure to repeat the experiments discussed in the first part of the paper does not, of course, in any way invalidate the results reported in the second part.

Bengt Hamilton, M.D.
The Department of Pediatrics, University of Chicago.

Obituary

BARNET E. BONAR, M.D.
1894-1937

Barnet E. Bonar, of Salt Lake City, Utah, died on Dec. 19, 1937, from fracture of the skull caused by a fall.

Dr. Bonar was born in Sterling, Ill., on April 5, 1894. His father was a practitioner of medicine there, who died when the son was a young student. Dr. Bonar graduated from the University of Wisconsin, completing his course in medicine at Rush Medical College, Chicago, in 1918. After this he served as intern at Cook County Hospital for eighteen months and was resident there for six months. He then took up work in pediatrics at Rush Medical College, where he taught for three years, 1920, 1921 and 1922. He then left Chicago and, with a group of his friends, went to Salt Lake City, where he had practiced ever since.

Besides being a member of the Utah State Board of Health for some time, he was one of the organizers of the Intermountain Pediatric Society and at one time was secretary of the Salt Lake County Medical Society. Dr. Bonar was a member of the American Academy of Pediatrics and of the American Pediatric Society. He was a leader in pediatrics in the intermountain region, although he did not confine his work entirely to that branch of medicine but did a considerable amount of obstetric practice. He was most interested in the newly born. About this subject he had written several articles and, in conjunction with Dr. Clifford G. Grulee, one book, The Newborn.[1] Just before his death, he became interested in fetal respiration and developed a technic for taking colored moving pictures of the live fetus in animals.

In a region where little advanced work in any branch of medical science is done, Dr. Bonar was continually working along investigative lines, but his efforts were by no means confined to this. He was one of the leading men in public health work in his state and was chairman of the Committees on Neo-Natal Morbidity and Mortality of the American Pediatric Society and of the American Academy of Pediatrics. He had acted in an advisory capacity with the Children's Bureau in Washington, and, although he was still a young man and was under some disadvantage because of the locality in which he had chosen to practice, he was rapidly attaining national recognition.

1. Grulee, Clifford G., and Bonar, Barnet E.: The Newborn, New York, D. Appleton & Company, 1926.

Dr. Bonar was a quiet, unassuming man with a most genial, kindly nature. He never became excited, yet he always stood up for what he thought to be right. All who knew him learned to respect and love him. He was indefatigable, often working in the early hours of the morning and for long hours at a stretch.

The pediatric profession will miss Dr. Bonar, not only because of his attainments but because of his personality.

News and Comment

GENERAL

Physicians Certified by American Board of Pediatrics.—The following physicians were certified by the American Board of Pediatrics on Nov. 15, 1937:

James Marvin Baty, Boston; J. Travis Bennett, El Paso, Texas; H. Arthur Berson, Boston; William Carter Black, San Diego, Calif.; Burtis B. Breese Jr., Rochester, N. Y.; Milo B. Brooks, West Los Angeles, Calif.; Leo B. Burgin, Boston; Benjamin Watson Carey Jr., Boston; Harry Ray Carson, Phoenix, Ariz.; Creed F. Cherry, Los Angeles; Harry F. Dietrich, Beverly Hills, Calif.; Bernard Fein, Newark, N. J.; Henry F. Gallagher, Los Angeles; Morris Gleich, New York; Thomas Lindner Harris, Los Angeles; Harry Horwitz, Oakland, Calif.; John P. Hubbard, Boston; Samuel Hurwitz, San Francisco; John Richard Jimerson, Long Beach, Calif.; Albert Preston Knight, Waverly, N. Y.; George Buchanan Kryder, Glendale, Calif.; Vernon William Lippard, New York; Barnett Lipson, Los Angeles; Hubert E. Long, Berkeley, Calif.; Russell W. Mapes, Beverly Hills, Calif.; Chester I. Mead, Bakersfield, Calif.; Francis T. O'Donnell, Wilkes-Barre, Pa.; Samuel E. Pasette, Los Angeles; Edwin F. Patton, Los Angeles; Charles H. Pettet, Los Angeles; Leo S. Radwin, Brooklyn; Maurice L. Ripps, Elizabeth, N. J.; Eli Charles Romberg, Boston; Edward Lee Russell, Santa Ana, Calif.; Ben Shapiro, New York; Albert W. Snoke, Rochester, N. Y.; Benjamin Spock, New York; Vivian Tappan, Tucson, Ariz.; John Orren Vaughn, Santa Monica, Calif.; Samuel M. Wishik, Flushing, N. Y.

All of these licentiates took the examination, as they all are required to appear for examination, regardless of their qualifications or of the length of time they have practiced. At the last two examinations forty applicants passed, fifteen failed and four were conditioned.

The following physicians were certified by the American Board of Pediatrics on Dec. 1, 1937:

Drs. Byron Alexander, Electric Mills, Miss.; Jay Morris Arena, Durham, N. C.; Harry Edgar Baldock, Charleston, W. Va.; Jacques H. Baumhauer, Mobile, Ala.; Lonita Mae Boggs, Greenville, S. C.; William H. Bradford, Dallas, Texas; Donald Froyd Cathcart, Atlanta, Ga.; William Copeland Cook, Columbus, Ga.; Richard G. Elliott, Lexington, Ky.; Charles Barton Etter, Memphis, Tenn.; Francis Allen Garbade, Galveston, Texas; Harvey F. Garrison Jr., Jackson, Miss.; Jacob Joseph Glaboff, Louisville, Ky.; Harris Hosen, Port Arthur, Texas; Guy Carleton Jarratt, Vicksburg, Miss.; Angus M. McBryde, Durham, N. C.; Paul R. Meyer, Port Arthur, Texas; James Carney Overall, Nashville, Tenn.; Walter Frank Qualtrough, Houston, Texas; Charles Finlay Rennick, El Paso, Texas; Samuel Jennings Roberts, Miami, Fla.; James Byron Snow, Oklahoma City; William Orren Vaughan, Nashville, Tenn.; Alvyn Waverly White, Pensacola, Fla.

All were examined. Thirty applicants took this examination. Of these, twenty-four passed, four failed, and two were conditioned in one or more subjects.

UNIVERSITY NEWS

Fellowship in Allergy.—The Asthma, Hay Fever and Allergy Foundation offers a twelve month fellowship in allergy in the Associated Foundations of the Laboratory of Anatomy of Western Reserve University.

The appointee will devote half his time to training and investigative work in connection with the developmental health inquiry being conducted by Prof. T. Wingate Todd and his associates and half his time to training in the clinical aspects of allergy at the asthma and hay fever clinic under Dr. Milton B. Cohen.

Candidates must be graduates of class A medical schools and must have completed at least one year of general internship and one year of special training in pediatrics. Preference will be given to those with additional special training in pathology, chemistry or immunology.

Since no maintenance is provided, fellows will receive $75 monthly. The next appointment will start July 1, 1938.

SOCIETY NEWS

American Orthopsychiatric Association.—The fifteenth annual meeting of the American Orthopsychiatric Association will be held at the Stevens Hotel, Chicago, on Feb. 24, 25 and 26. Dr. Norvelle C. LaMar, 210 East Sixty-Eighth Street, New York, is the secretary of the society.

CORRECTION

In the abstract of the article by F. Lisi (*Lattante* **8**:75 [Feb.] 1937) which appeared in the November issue (AM. J. DIS. CHILD. **54**:1126, 1937), "4.3 per thousand" in the second line of the paragraph bearing the italic side heading "Syphilitic Infantile Mortality and Morbidity" should be "4.3 per ten thousand."

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

THE CLINICAL USE OF DESOXYCHOLATE AND DESOXYCHOLATE-CITRATE-AGARS—NEW CULTURE MEDIA—FOR THE ISOLATION OF INTESTINAL PATHOGENS. M. PAULSON, Am. J. M. Sc. **193**:688 (May) 1937.

New culture mediums, designated as desoxycholate and desoxycholate-citrate agars, have been applied in clinical research and in the routine clinical investigation of bowel disturbances. Both mediums, used simultaneously, inhibit to a degree not encountered in other culture methods all gram-positive intestinal bacteria. Desoxycholate-citrate agar inhibits practically all of the common intestinal nonpathogens, permitting the growth only of Flexner dysentery bacilli, typhoid, paratyphoid A and B, and other paratyphoid bacilli, Bacillus pyocyaneus and Proteus vulgaris. Proteus grows as a nonspreading colony. Desoxycholate agar offsets, in a measure, the limitations of the aforementioned agar by permitting the growth of all gram-negative but no gram-positive organisms. Thus, the concomitant use of both mediums, one complementing the other, each in part overcoming the limitations of the other, is regarded as a distinct advance in the routine clinical study of bowel disturbances from a bacteriologic standpoint.

HENSKE, Omaha.

THE EFFECT OF LECITHIN ON STREPTOCOCCAL AND STAPHYLOCOCCAL HEMOLYSIN. LOUIS WEINSTEIN, J. Infect. Dis. **60**:209 (March-April) 1937.

In substance, the following facts were discovered when lecithin was added to mediums in proper amounts. When the ratio of lecithin was 1 cc. to less than 50 mg. of medium, the growth of streptococci was luxuriant, but hemolysis was prevented. When cholesterol was used alone, hemolysis occurred; when lecithin and cholesterol were used in combination, hemolysis likewise occurred. This illustrates that hemolysis is inhibited by lecithin.

JOHN A. TOOMEY, Cleveland.

A COMPARISON OF MENINGEAL AND OTHER STRAINS OF H. INFLUENZAE. DOROTHY WILKES-WEISS, J. Infect. Dis. **60**:213 (March-April) 1937.

Wilkes-Weiss found that there was a slight morphologic difference between influenzal organisms isolated from the blood and those isolated from the spinal fluid of patients ill with meningitis in that the former were very short and the latter were thread-like in form. Biochemical studies showed that thirty-eight of forty-three meningeal strains and ten of nineteen respiratory strains produced indol. Therefore, this test cannot be used to identify meningeal strains. Serologic tests seemed to show that there was some degree of antigenic homogeneity among meningeal strains of Haemophilus influenzae.

TOOMEY, Cleveland.

A STUDY OF SOME OF THE PROPERTIES OF THE TOXIC SUBSTANCES PRODUCED BY SALMONELLA PARATYPHI A AND B. RUTH E. GORDON and C. N. STARK, J. Infect. Dis. **60**:238 (March-April) 1937.

Gordon and Stark show that the potency of the toxins produced by Salmonella paratyphi A and B varies and that there is some relationship between the toxicity and the number of organisms present in the growth medium. Of interest is the fact that this toxic filtrate could be stored at 10 C. for two months and at 20 C. for one month without decreasing its toxicity, while simple storage at 40 C. for two weeks and at 50 C. for one week markedly decreased its potency.

JOHN A. TOOMEY, Cleveland.

Metabolism; Infant Feeding; Milk and Other Foods

NUTRITIVE VALUE OF SOYA-BEANS: IS IT A COMPLETE FOOD? N. K. BASU, Indian J. Pediat. **4**:83 (April) 1937.

Soya beans contain 40 per cent protein (almost all important amino-acids essential for growth being present), 20 per cent fat and 25 per cent carbohydrate, lecithin and vitamins A, B and D. Eric Reid considers dried powder from soya bean and egg yolk an effective substitute for cow's milk. Prompted by these facts, Basu investigated the biologic value of soya beans on white rats and found that soya bean powder alone failed to produce normal growth and that soya bean powder in combination with milk powder, bread, puffed rice or vegetables did produce satisfactory growth. The best results in growth were obtained when soya bean powder and milk powder were administered together, but reproduction in these animals was not at all satisfactory; even in those cases in which actual reproduction took place the young did not survive for more than a day or two. Basu concludes that soya bean is not a complete food and that protein from animal sources is much more important biologically than protein obtained from vegetable sources.

GONCE, Madison, Wis.

THE BLOOD SEDIMENTATION RATE IN RELATIONSHIP TO FEEDING AND NUTRITION. P. LUCIANI, Arch. ital. di pediat. **5**:99 (April) 1937.

Breast-fed infants have a sedimentation rate of from 3 to 5 mm. in the neonatal period (the first month of life) and of from 6 to 10 mm. throughout the rest of the first year. This conclusion is based on a study of thirty-two infants. A group of sixteen babies less than 1 year old on mixed feedings had rates of between 11 and 13 mm. A similar group of ten babies on entirely artificial feeding had rates of between 20 and 21 mm. Acute infections increased the rate no matter what the feeding. Normal babies in the second and third year had rates of from 11 to 13 mm. Atrophic, hypotrophic and rachitic babies had rates of from 16 to 20 mm. The author uses a new micromethod employing the "index of Katz."

DOOLEY, New York.

THE "CUNCTATROPHIC" INFANT. E. HAINISS, Lattante **8**:263 (May) 1937.

The cunctatrop is one whose growth is delayed and slow. The infant on mother's milk should have feces with a p_H between 5 and 5.6 if there has been optimal action of Bacteroides bifidus in the intestines. Infants who have not been gaining properly in weight (cunctatrops) are often found to have stools less acid than p_H 5.6.

HIGGINS, Boston.

TECHNIC OF ARTIFICIAL FEEDING; GIVING OF MILK BY THE CUP. A. BORRINO, Lattante **8**:267 (May) 1937.

Borrino favors the giving of artificial milk formulas by cup or spoon rather than by the bottle and nipple. She has devised a porcelain cup holding from 180 to 200 cc., with a protruding tubelike spout; this is readily adaptable for feeding even new-born infants. The cups are easily washed and sterilized; there are several designs in color, either flowers or animals, which serve to identify the cup and feeding.

HIGGINS, Boston.

TOBACCO AND NURSING: NOTE ON THE HYGIENE OF THE NURSLING. A. MUGGIA, Lattante **8**:294 (May) 1937.

A breast-fed infant had been gaining well for two months; then he ceased to gain, had signs of fat indigestion, restlessness, insomnia and anemia; the pupils

were miotic; the heart seemed normal, although the pulse was intermittently rapid. Pancreatin and some artificial feedings relieved the indigestion but not the other symptoms. When it was discovered that both the father and the mother smoked excessively in the room of the child, nicotine poisoning was suspected. Smoking in the child's room was discontinued, and the mother was told to abstain from tobacco. The child rapidly recovered from his symptoms, and the diagnosis of nicotine poisoning seemed to be proved.

Muggia reviews the observations of Italian clinicians and scientists on the effects of tobacco on the woman, the fetus and the nursing infant. Infants born to women who work in tobacco factories are usually of small size and poor resistance. Overindulgence in tobacco may lead to premature birth. The circulation of the mother and the nursing child are definitely affected by tobacco as shown by palpitation, tachycardia and increase in blood pressure. The fetal heart rate has been reported to increase from 5 to 75 beats per minute ten to twenty minutes after the mother has finished smoking.

Since nicotine is excreted through the milk, Muggia feels that nursing mothers should not use tobacco.

HIGGINS, Boston.

EXPERIMENTAL STUDIES ON SOME BIOLOGIC PROPERTIES OF FOOD PRESERVED AT VERY LOW TEMPERATURES. C. COCCHI, Riv. di clin. pediat. **35**:429 (May) 1937.

Observations were made on rats and guinea pigs. The animals were put on diets deficient in vitamins. When the animals began to show symptoms of deficiency they were given, in addition to their previous diet, foods which had been frozen to a temperature of —60 C. Milk was used to supply vitamins A and D, beer to supply vitamin B and cabbage to supply vitamin C. The food which had been frozen was quite as successful in overcoming the signs of vitamin deficiency as was fresh food. The animals which were put on the food which had been frozen did not, however, gain in weight quite so fast as the animals that were given fresh food.

HIGGINS, Boston.

INFLUENCE OF DIET ON BLOOD SUGAR. A. PANOFF, Monatschr. f. Kinderh. **70**:199 (May) 1937.

In eight patients with diabetes Panoff tried the effects of various dietetic measures. He found that excess of levulose always led to continuous hyperglycemia. Following ingestion of protein there was usually a rise with a relatively rapid fall, but there was no typical curve. Fat did not lead to increase. The addition of various carbohydrates also led to varying results. The study shows nothing tangible.

GERSTLEY, Chicago.

RHYTHM IN EXCRETION OF ACETONE. T. ROHLEDER, Monatschr. f. Kinderh. **70**:212 (May) 1937.

In a 9 year old boy with glycogenosis the excretion of acetone in the urine seemed to follow a certain rhythm. It was lowest during the night and during the afternoon. The highest values were observed in the mornings about 10 o'clock, two hours after breakfast.

GERSTLEY, Chicago.

EFFECT OF FAT AND GLYCERIN ON BLOOD CONTENT OF SUGAR. M. B. MACLEAN, Monatschr. f. Kinderh. **70**:220 (May) 1937.

Experiments were conducted in which olive oil and glycerin were fed. Olive oil led to no increase in blood sugar. Glycerin always did. Evidently, ordinary fat in the food does not change to dextrose.

GERSTLEY, Chicago.

Vitamins; Avitaminoses

ENZYMIC EFFICIENCY IN AVITAMINOSIS: VII. PEPTIC DIGESTION IN VITAMIN B DEFICIENCY. B. SURE and R. T. HARRELSON, Am. J. Digest. Dis. & Nutrition **4**:177 (May) 1937.

Rats were used, with carefully considered controls. The data show that there is no significant change in the rate of peptic digestion when comparisons are made with litter mate controls of the same sex and restricted to the same plane of nutrition. This is true in deficiency of the vitamin B complex and in deficiency of vitamin B, associated with paralysis of varying degrees.

MORRISON, Savannah, Ga.

A CHEMICAL PECULIARITY OF PELLAGRA BLOOD. SECOND REPORT. C. H. CAMPBELL and S. R. SHAVER, Am. J. M. Sc. **193**:658 (May) 1937.

In a preliminary note the author reported observations relative to a rapid decolorization of iodine by the erythrocytic mixture of pellagrous blood. In that study it was found that with a standard technic pellagrous blood reduced a solution of iodine at a constantly greater rate in comparison with normal controls and in comparison with samples of blood from patients with a variety of nonpellagrous pathologic conditions. It was proposed that this reaction might be of clinical value in the diagnosis of pellagra.

The modification in technic advocated by Sotelo is of definite value as a time-saving procedure. The authors' experience continues to show that the erythrocytic mixture of pellagrous blood reduces iodine more rapidly than normal or other pathologic specimens.

HENSKE, Omaha.

VITAMIN A DEFICIENCY IN THE RHESUS MONKEY: STUDIES ON THE GASTRO-INTESTINAL TRACT, THE BLOOD AND NERVOUS SYMPTOMS. ELIZABETH VERDER and ELIZABETH PETRAN, J. Infect. Dis. **60**:193 (March-April) 1937.

Verder and Petran present the results of an excellent experimental study on vitamin A deficiency. Seven Macacus rhesus monkeys were used, five of which received plenty of vitamin A and two of which were fed a diet deficient in this vitamin. The authors conclude that other than severe diarrhea, which lasted from eight to twenty-four weeks, a slight increase in the total number of leukocytes and in the average number of polymorphonuclear leukocytes and the possibility of night blindness in two animals and ulcerative colitis in two others, there was not much difference between the vitamin-protected animals and the unprotected animals. The mucosa of the colon of one animal had shallow ulcers, and that of the other animals in the same group was hyperemic but did not contain grossly visible ulcers.

JOHN A. TOOMEY, Cleveland.

ETIOLOGY AND PATHOLOGY OF RICKETS. A. B. MARFAN, Lattante **8**:239 (May) 1937.

Between 1919 and 1927, three important discoveries enriched the history of rickets: (1) the production of experimental rickets in rats, (2) the antirachitic action of ultraviolet rays and (3) the antirachitic action of viosterol.

From these discoveries American investigators have proposed a theory that (1) the diminution of inorganic phosphorus in the blood is the direct cause of rachitic lesions and (2) this hypophosphatemia is due to absence of ultraviolet rays.

Marfan feels that the facts do not permit absolute acceptance of this theory and presents his own theory: (1) Vitamin D is a definite substance (viosterol) and (2) the lack of it must be accompanied by infection or intoxication to produce rickets.

HIGGINS, Boston.

TREATMENT OF SPASMOPHILIA WITH CRYSTALLINE VITAMIN B_1. F. WIDENBAUER, Monatschr. f. Kinderh. **70**:82 (April) 1937.

Ten patients with spasmophilia were treated with injections of vitamin B_1. Four recovered rather definitely, and four others presumably recovered. The result was doubtful in one case, and in another treatment was unsuccessful.

GERSTLEY, Chicago.

INVESTIGATION OF AVITAMINOSIS-A IN STANDARD DIET GROUP. C. KOBAYASHI and S.-Y. LI, J. Orient. Med. **26**:753 (April) 1937.

Kobayashi and Li investigated the relation of a standard diet adopted by a group of Manchurians in Mukden to the incidence of avitaminosis A. Of 982 subjects on this diet, xerophthalmia was found in 286 (29.1 per cent) and keratomalacia in 2. Examination of the diet revealed a pronounced deficiency in foods rich in vitamin A.

KATO, Chicago.

Hygiene; Growth and Nutrition; Public Health

INFLUENCE OF LIFE IN LARGE CITIES ON THE HEALTH OF CHILDREN. P. NOBÉCOURT, Gaz. d. hôp. **110**:621 (May 12) 1937.

This is a medical school lecture, emphasizing that besides climatic factors (dust, carbon monoxide, reduction in ozone, lessening of the positive charge on the particles in the air, reduction in infra-red and ultraviolet rays) and hygienic factors (noise of traffic, tendency to keep late hours and excitement) which affect all children, one has to consider the endogenous characteristics of the patients (inadaptability to city life) to explain the remarkably beneficial effect on some children of a sojourn in the country.

KAJDI, Baltimore.

NOTES ON POLITICAL DEMOGRAPHY. S. MAGGIORE, Lattante **8**:273 (May) 1937.

This article was inspired by the drop in the birth rate in Italy. There were 989,351 live infants born in 1935, 955,193 in 1936 and a further decrease in 1937; a decrease is found in practically each province and city. In the northern provinces the birth rate was lower, but this was counterbalanced by a lower death rate. The excess of births over deaths per thousand in all Italy in 1922 was 12.2; in 1935, 9.4.

On analyzing the three main causes of infant mortality—(1) congenital diseases and malformations, (2) acute gastro-intestinal diseases and (3) acute respiratory diseases—it appears that the second affords the most opportunity for active work in lowering the death rate. Fifty-five thousand Italian children under 2 years of age died of enteritis in 1935. Italy had the seventh highest infant mortality rate among twenty-four countries.

HIGGINS, Boston.

THE BIOTYPOLOGIC CARD AS A BASIS FOR THE BETTERMENT OF FUTURE GENERATIONS. CARRASCO M. FRANCISCO, Bol. Inst. internac. am. de protec. a la infancia **10**:537 (April) 1937.

Francisco, referring to Law 54, passed in 1928 in Panama, which exacts a prenuptial certificate, considers that such a requirement is a great advance toward the adoption of eugenic principles tending to improve new generations. However, the obligation of obtaining this certificate does not pertain to women, and those who passed the law did not foresee the necessity of creating a gratuitous prenuptial clinic with the necessary equipment for all sorts of examinations.

Another imperfection of this law is that it does not include illegitimate children, and since three fourths of the children in Panama are born out of wedlock, the number of those favored by the law is limited.

In order to correct the deficiencies of the prenuptial certificate, the teaching of eugenic culture in the home and in all teaching centers should be emphasized and

a national preventorium should be created with physicians of acknowledged capacity in charge and with the personnel and equipment necessary to make a biotypologic card of all the inhabitants, so that the record, started at birth, can be continued in the home, the school, the university, the workshop and the office.

FROM THE EDITOR'S SUMMARY.

THE BOND OF MOTHERHOOD. WALTER PIAGGIO GARZÓN, Bol. Inst. internac. am. de protec. a la infancia **10**:550 (April) 1937.

Garzón speaks of the elevated function of maternity and recalls the vital bond that unites the mother with the child, in a symbiotic form, first during pregnancy and later during the nursing period. As to this point, he states that "nursing the mother is most important of all" and that according to Roussel "all that tends to separate the child from its mother places it in a state of suffering and in danger of death."

FROM THE EDITOR'S SUMMARY.

INFANT MORTALITY IN MONTEVIDEO. JULIO A. BAUZÁ, Bol. Inst. internac. am. de protec. a la infancia **10**:563 (April) 1937.

Bauzá discusses infant mortality in Montevideo, the capital of Uruguay. A slight decrease occurred in the period from 1931 to 1935, the average rate of which was 105 deaths per 1,000 live births. After Buenos Aires, Montevideo has the lowest infant mortality of any city in Latin America.

FROM THE EDITOR'S SUMMARY.

OPEN AIR SCHOOLS AND COLONIES IN NORTH AND SOUTH AMERICA. EMILIO FOURNIÉ, Bol. Inst. internac. am. de protec. a la infancia **10**:580 (April) 1937.

This article is a résumé of the open air school in the various countries of the Americas. It is suggested that every country should have a national committee to centralize the course of all open air activities, thus uniting efforts, perfecting methods and collecting proper material. However, such a committee should not monopolize the action of private organizations, which should be promoted and helped so that the number of colonies and camps might increase. Furthermore, an American international committee of open air schools and other activities should be organized.

LESLIE, Evanston, Ill.

OPEN AIR SCHOOLS IN THE UNITED STATES. MARY WALDO TAYLOR, Bol. Inst. internac. am. de protec. a la infancia **10**:632 (April) 1937.

This article is a résumé of the open air schools in the United States. There is an indication that as health measures and preventive programs become more general, there will be less need for the curative features of the open air school. This day has not yet arrived, however, and open air schools and open window rooms continue to be needed where the condition of pupils is such that their welfare demands it or where there is need of demonstrating to the community the results that may be expected through proper health measures.

LESLIE, Evanston, Ill.

New-Born

TRAUMA IN THE NEW-BORN. W. M. HARTSHORN, New York State J. Med. **37**:869 (May 1) 1937.

In this lecture presented at the Graduate Fortnight in New York City, Hartshorn gives brief histories of cases to illustrate the various types of trauma.

AIKMAN, Rochester, N. Y.

A Case of Lipophagic Granuloma and Sclerema Neonatorum. F. J. Eichenlaub and I. L. Sandler, South. M. J. **30**:527 (May) 1937.

The authors present a case of combined lipophagic granuloma and sclerema neonatorum. The granuloma developed first and was diagnosed as subcutaneous fat necrosis by biopsy. The second disease developed after otitis media and probable bronchopneumonia caused inanition and dehydration. In this state, true sclerema neonatorum developed. The authors believe this to be the first instance in which both conditions occurred simultaneously in the same patient.

Schlutz, Chicago.

Salmonella Infecton in the New-Born. Angel A. Aballi and Others, Bol. Soc. cubana de pediat. **9**:123 (April) 1937.

Aballi and his co-workers present a series of twelve cases of infection with Salmonella aertrycke in new-born infants, which appeared as an epidemic outbreak at the Maternity Hospital in Havana during November and December 1936. No definite source of the infection was discovered. The majority of the affected infants were breast fed. Most of them weighed 7 pounds (3,175 Gm.) or less. The onset was usually abrupt on the sixth to the eighth day, with high fever, which later followed a remittent course. Diarrhea, with blood and mucus in the stools, was generally observed and often led to marked anhydremia. Meningo-encephalitic manifestations appeared later and became the most prominent feature of the condition. They were associated with cloudy or purulent spinal fluid from which the organisms could be recovered in pure culture. These could also be demonstrated in the blood and stools. Near the end, petechial hemorrhages appeared on the skin. The mortality was 100 per cent.

Postmortem examination in these cases revealed a severe meningo-encephalitic process which was often of the hemorrhagic type. Iliocolitis with slight ulcerations was usually present. The liver proved to be the site of severe toxic hepatitis, and the kidneys also revealed marked toxic changes. In other internal organs and in the skin there were petechiae and purpuric hemorrhages.

Aballi and his associates do not believe that any of the present methods of therapy would offer a chance of cure. They assume that the transmission of the disease occurred through contact or through contaminated utensils. The outbreak was controlled by complete isolation.

Schlutz, Chicago.

The Syndrome of Hemorrhagic Disease of the New-Born. Francisco Carlos Grelle, J. de pediat., Rio de Janeiro **4**:141 (April) 1937.

On the basis of 170 autopsies on new-born infants, Grelle states that cerebral lesions are found both in the brain and in the meninges. Various other organs of the body likewise show hemorrhage. This type of hemorrhage is obviously not due to obstetric trauma but must represent a hydrodynamic mechanism that acts on the fragile capillary vessels. Grelle therefore proposes that the condition be called in general the syndrome of hemorrhagic disease of the new-born.

Sanford, Chicago.

Chylothorax of the New-Born. T. Rohleder, Monatschr. f. Kinderh. **70**:208 (May) 1937.

A case is reported, with roentgen and autopsy observations. The child lived only a few days. No cause was found for the chylothorax.

Gerstley, Chicago.

THE WEIGHT OF THE BABY AT BIRTH. N. F. GREGERSEN, Acta obst. et gynec. Scandinav. **17**:75, 1937.

In 1875 Ingerslev, of Copenhagen, found the average weight of 3,450 new-born babies delivered at term by healthy mothers to be 3,333.5 Gm. Under similar conditions in the same city, the average weight of 2,037 new-born infants for the period 1932 to 1934 was found to be 3,531.7 Gm. This is an average increase of 200 Gm. in weight.

ADAIR and POTTER, Chicago.

Acute Contagious Diseases

HISTOPATHOLOGIC STUDIES IN EXPERIMENTAL POLIOMYELITIS. J. A. LUHAN, Arch. Neurol. & Psychiat. **37**:479 (March) 1937.

Luhan has studied the pathologic aspects of poliomyelitis in seventeen immature monkeys, particularly to get further information about the route of spread in the central nervous system. He concludes that the major spread of the virus is along the channels within the neuraxis rather than through the cerebrospinal fluid or the meninges.

BEVERLY, Chicago.

PERIVENOUS CHANGES IN ACUTE ENCEPHALITIS ASSOCIATED WITH VACCINATION, VARIOLA AND MEASLES. K. H. FINLEY, Arch. Neurol. & Psychiat. **37**:505 (March) 1937.

This is an excellent article on the pathologic changes associated with vaccination, variola and measles. The author concludes that the distribution of the lesions is primarily along the venous channels.

BEVERLY, Chicago.

PREVENTIVE IMMUNIZATIONS IN CHILDHOOD. J. S. WALL, Arch. Pediat. **54**:198 (April) 1937.

Wall reviews the various procedures for actively and passively immunizing children. His working program consists of vaccination against smallpox at the age of from 3 to 6 months; vaccination against whooping cough followed by immunization against diphtheria, at from 6 to 9 months; protection against scarlet fever in special instances during the second year. Typhoid vaccination is given at 5 to 7 years or earlier if environmental factors favor the chance of infection.

Passive immunization is always administered against tetanus if the wounds are of suspicious origin. Immunization to modify measles should be administered to all children exposed to the disease.

Every physician in his daily work should employ routine immunization against these various diseases if he is to defeat the exploitation of pediatrics by the state under the guise of public health.

ORR, Buffalo.

TRIGEMINOFACIAL CERVICAL REACTION WITH COMPLETE INVOLVEMENT OF THE FACIAL NUCLEUS IN ANTERIOR POLIOMYELITIS. S. M. WEINGROW, Arch. Pediat. **54**:231 (April) 1937.

A case of anterior poliomyelitis involving the nucleus of the right facial nerve is presented. Tapping the right side of the face did not result in contraction of the facial muscles but in a jerk of the head to the right side, accompanied by a sudden upward movement of the right shoulder. This reaction is an indication that one of the componennts usually involved in a particular aspect of craniocervical activity, i. e., the facial, has been removed from participation in the activity of the particular craniocervical muscle group of that side because of paralysis of some muscles that it supplies—for example, the platysmamyoides.

ORR, Buffalo.

THE TREATMENT OF MENINGOCOCCIC MENINGITIS WITH SULFANILAMIDE. F. F. SCHWENTKER, S. GELMAN and P. H. LONG, J. A. M. A. **108**:1407 (April 24) 1937.

In a report of their experience with the use of sulfanilamide in ten patients with meningococcic meningitis, Schwentker, Gelman and Long state that while the number of patients is too small to permit any definite conclusions the response to the treatment was good in all and seemed quite comparable to that caused by the specific antiserum.

BONAR, Salt Lake City.

NEWER ASPECTS OF THE WHOOPING COUGH PROBLEM. J. A. TOOMEY, J. Pediat. **10**:472 (April) 1937.

Clinically pertussis may be divided into the incubational, catarrhal, early paroxysmal, whooping and convalescent stages. During the incubational, catarrhal and early paroxysmal stages of the disease, Haemophilus pertussis in phase I is easily isolated. It is during this period that the disease is most contagious. When the patient is well into the paroxysmal and whooping stages, the patient being then the sickest, it becomes more and more difficult to find bacilli of phase I. During the whooping state sticky mucoid balls of exudate are coughed up (composed of mucomycelium). It is this sticky material, produced during the growth of the organism, which causes the whoop. The disease-producing organism in phase I, obtained early in the disease, will not produce this material in vivo or when grown in vitro. Only after the organism becomes acclimated to the host is it able to produce the exudate in amounts sufficient to cause the whoop. The phase I type of organism which produces disease in man becomes acclimated to the host and changes to the fixed or resistant state of its existence and in this state thrives and grows on nearly any experimental medium. When grown in vitro this organism will produce a sticky mucoid material similar in all physical characteristics to that coughed up by children after a whooping spell. This mucoid material is not the soluble toxin and cannot be confused with Krueger's endo-antigen nor has it anything in common with the freshly isolated organism. It is a new substance, first grown by the author, a product produced during the course of bacillary growth just as the toxin of diphtheria is produced during the course of diphtheria by the diphtheria organism. The toxin of the latter causes diphtheria; the exudate of the fixed phase organism brings about the whooping cough stage.

Since it is thought that a clinical cure for pertussis is brought about when this sticky material is counteracted and disposed of, the author felt that actual attacks of the disease might be shortened by injections of this metabolic material. At first large doses were injected. The material contained phase IV organisms in great number and caused local reactions and fever. The dosage was then decreased, the product purified and the organisms omitted. Eighty children, all under 3 years, were treated with it. In general there were fewer paroxysms and whoops after the injections, and when the injections were given early enough the whoops were almost entirely abolished. Local reactions were slight. Only one death occurred in this series from the disease. The results obtained were suggestive, but hundreds of patients must be treated before definite conclusions can be drawn.

RAUH, Cincinnati.

VITAMIN C AND DIPHTHERIA TOXIN. A. SIGAL and C. G. KING, J. Pharmacol. & Exper. Therap. **59**:468 (April) 1937.

Sigal and King conclude that vitamin C per se has no detoxifying action on diphtheria toxin. When the two are mixed, the acidity of the vitamin does inactivate the toxin, but this does not occur when the acidity is buffered. Guinea-pigs were not protected by vitamin C unless the p_H of this was lowered considerably.

PILCHER, Cleveland.

COINCIDENCE OF CHICKEN POX AND LYMPHATIC LEUKEMIA. A. A. HOLBROOK, New England J. Med. **216**:598 (April 8) 1937.

The following case is presented because it raises a number of interesting questions as to the coincidence of varicella and lymphatic leukemia in the same patient, the etiologic relation between varicella, generalized herpes zoster and leukemia, the skin manifestations in lymphatic leukemia, the differential diagnosis between the vesicles of herpes zoster and those which are specific for lymphatic leukemia, and the blood picture in varicella. All except the last are discussed.

A 17 year old white boy complained chiefly of an itching eruption over the face, scalp, trunk, upper part of the arms and thighs. The temperature was 102 F. Small shallow ulcers, looking like broken vesicles, were observed on the gums. The cervical nodes below the ears and the angles of the jaw and one inguinal node were swollen and tender. The diagnosis of chickenpox was confirmed by the public health authorities.

During the first week the patient exhibited successive fresh crops of the vesicular eruption. The ulcerations in the gums became deeper and painful, and superficial sloughing occurred; a direct smear showed the spirilla and fusiform bacilli of Vincent's infection.

The hemoglobin decreased from 65 to 47 per cent; the red blood cells, from 3,800,000 to 2,700,000. The white blood cells were 19,500; then they rose to 27,300, went down to 4,100 and later up to 63,700. Polymorphonuclears were 4 per cent; they then increased to 33 per cent and later decreased to 1 per cent, while the lymphocytes varied between 96 and 54 per cent. The boy lived about a month. The diagnosis was confirmed by autopsy. Holbrook was able to find only three similar cases recorded in the literature. GENGENBACH, Denver.

CURRENT PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **52**:465 (April 16) 1937.

For the period of February 28 to March 27 influenza decreased in all sections. There were 772 cases of meningococcic meningitis, which is less than for the same period in 1936 but more than for the same period in 1935. Measles, scarlet fever and diphtheria continued low. Typhoid fever was higher, with 423 cases, as was smallpox, with 1,920. The average mortality was 13.1 per thousand.

SANFORD, Chicago.

SEASONAL PATTERNS AND TRENDS OF COMMUNICABLE DISEASES. R. OLESEN, Pub. Health Rep. **52**:609 (May 7) 1937.

By charting the monthly incidence of various contagious diseases Olesen finds that irrespective of individual years the contagious diseases follow a continuous pattern. The curve for diphtheria is low in summer, reaches a peak in fall, sinks in December and rises again in January; that for influenza is low in the summer, rises in the fall and comes to a peak in midwinter. The peak of measles is in the spring, as is that of meningococcic meningitis. The curve for smallpox is at a peak in late winter and spring and low in summer, while that for typhoid fever is low all year except in late summer. The curve for poliomyelitis is low all year except in late summer, and that for scarlet fever is low in the summer and slowly rises to a peak in late winter and spring. The observations cover the years 1928 to 1936.

SANFORD, Chicago.

INTRA-EPIDERMIC VACCINATION. E. R. PEIRCE, Brit. M. J. **1**:1066 (May 22) 1937.

The principal difference in this method is that instead of tapping the skin through a drop of virus, as is customary today, the author inserts a needle through the drop into the epidermis. He feels that this method has a distinct advantage over any other customary method. ROYSTER, University, Va.

CHEMOTHERAPY OF STREPTOCOCCAL INFECTIONS WITH P-BENZYLAMINOBENZENE-SULPHONAMIDE. B. A. PETERS and R. V. HAVARD, Lancet **1**:1273 (May 29) 1937.

The administration of this derivative of sulfanilamide to patients with scarlet fever reduced the number having complications from 56 per cent (control series) to 35 per cent. The drug seems to affect chiefly the invasive stage, and results might be better if it could be given earlier. The possibility of a combination of drug and serum being more effective is also being considered. In erysipelas the spread of the disease was arrested in twenty-four hours in all of the forty-seven cases, and the temperature was normal within twenty-four hours in thirty-one of the patients.

LANGMANN, New York.

SIMULTANEOUS SCARLATINA AND MEASLES. N. A. ZUCKERMANN, Arch. de méd. d. enf. **40**:226 (April) 1937.

The appearance of coincident infections, particularly measles and scarlet fever, with one influencing the complications of the other, is infrequent enough to warrant publication. An epidemic of measles was reported from the scarlet fever division of the Soviet Hospital at Winniza; abundant opportunity was afforded the staff to observe the simultaneous evolution of these exanthems and to appraise the value of antimorbillous serum. The theory commonly accepted that these two contagions are antagonistic was readily disproved. It was established that scarlatina and measles could be encountered in most unusual combinations and at any stage of infection. In the series noted among the children isolated in the scarlet fever pavilion there were eleven patients with measles; of these, three were boys and eight were girls, the ages ranging from 1 to 7 years. Serum was employed in the treatment of seven, the average dose being from 50 to 100 cc.; it was obtained from the blood of pregnant women. Notwithstanding the exhibition of this prophylactic, all of the exposed children contracted measles, and the epidemic continued until an initial dose of 100 cc. was given all newly admitted children.

The complications of scarlet fever were greatly magnified with the invasion of measles, particularly those involving the kidney and the middle ear, but they promptly subsided with the disappearance of the invader.

AMESSE, Denver.

INJECTION OF THE VIRUS OF VARICELLA INTO THE CHORIONIC-ALLANTOIC MEMBRANE OF THE CHICK EMBRYO. J. DE CASTRO TEIXEIRA, Compt. rend. Soc. de biol. **121**:779, 1936.

Into the chorionic-allantoic membrane of a chick embryo which had been incubated from twelve to thirteen days was injected according to Goodpasture's method the vesicular material of chickenpox. Repeated injections were sometimes necessary. In a few days the exterior surface of the membrane showed small irregular nodules, each surrounded by a white area, spreading from the inoculated point.

WAHL, Cleveland.

FLACCID PARALYSIS FOLLOWING STOVARSOL TREATMENT OF AMEBIC DYSENTERY. L. BABONNEIX, M. LÉVY and L. GOLÉ, Rev. neurol. **63**:191 (Feb.) 1935.

A 7 year old boy had severe amebic dysentery. Emetine, acetarsone (stovarsol) and neoarsphenamine were given, with lessening of the symptoms after four weeks of treatment. During the sixth week pains in the extremities came on, and extensive flaccid paralysis appeared. The authors reluctantly come to the conclusion that the large doses of stovarsol were responsible for the damage.

DAFFINEE, Boston.

POSTDIPHTHERITIC HEMIPLEGIA AND POLYNEURITIS. C. I. URECHIA and RETEZEANU, Rev. neurol. **63**:277 (Feb.) 1935.

A girl of 7 years had diphtheria. Serum was administered twice. Ten days after the onset she was allowed to go home to the care of the family physician. Seven days later she presented right hemiplegia. She also showed motor aphasia and evidence of peripheral nerve damage in the limbs and throat.

A month after the onset she choked on some food and died. The observations at autopsy are given. The principal lesion was left lenticular degeneration.

DAFFINEE, Boston.

THE SKIN CAPILLARIES IN MEASLES. G. ERNANDEZ, Riv. di clin. pediat. **35**:344 (April) 1937.

Ernandez observed the capillaries of the skin in the mastoid region microscopically during the preexanthematous, the exanthematous and the postexanthematous stages of measles. Distinct changes in the shape, size, number and color of the visible vessels were noted during the preexanthematous period. If properly interpreted, they may be used as early diagnostic evidence of measles. The changes completely disappear after the infection has subsided.

HIGGINS, Boston.

WHOOPING COUGH COMPLICATED BY PURPURA. E. CORREA DE AZEVEDO and MANGEL SALDIV NETO, Arch. de pediat., Rio de Janeiro **9**:209 (April) 1937.

A 3 year old boy with pertussis presented hemorrhagic symptoms. The platelet count was found to be 80,000, with a bleeding time of thirty minutes and a coagulation time of four minutes. Vaccine therapy was continued for the whooping cough, and maternal blood was injected for the purpura. The boy recovered. Four months later the platelet count was 270,000, and the bleeding time had fallen to two minutes. On the basis of the thrombocytopenia, the authors believe this to be a true case of purpura and not a manifestation of the pertussis.

SANFORD, Chicago.

THE IMPORTANCE OF ACTIVE IMMUNIZATION IN COMBATING DIPHTHERIA. J. WUESTENBERG, Med. Klin. **33**:531 (April 16) 1937.

Active immunization against diphtheria is gaining a firm foothold in Germany. Compulsory immunization by one dose of alum-precipitated toxoid during the year after vaccination and a second dose shortly before the subject reaches school age is recommended.

SIEMSEN, Chicago.

CAN ONE HAVE WHOOPING COUGH TWICE? D. GAJZÁGÓ and O. GÖTTCHE, Monatschr. f. Kinderh. **70**:64 (April) 1937.

Five cases are reported in which it was almost certain that whooping cough occurred in early childhood and again in adult life.

GERSTLEY, Chicago.

A NOTE ON THE HISTORY OF VACCINATION AGAINST SMALLPOX. ERNST SCHRÖDER, München. med. Wchnschr. **84**:654 (April 23) 1937.

Pastor Ernst Schröder contributes an interesting letter relating the practice of vaccination against smallpox some time before Jenner's original experiment. The letter was written by the author's great grandfather, Matthius Claudius, to his sister Anna Claudius, the wife of Max Jacobi, a physician. The letter is dated 1800 and relates a conversation between Claudius and his pastor. Thirteen years before the pastor's father had visited a farmer and found that his five children had swollen arms as a result of vaccination with material from cowpox lesions. For many years this farmer had vaccinated the children in his family who had

not had smallpox. The sixth child was not vaccinated and contracted smallpox while in another village. He returned home and was in contact with the vaccinated brothers and sisters, but none contracted smallpox.

Later in his letter Claudius states that if it is true that those who have cowpox recover without ill effects and seem to be immune to smallpox, it would be permissible to inoculate children with material from lesions of human beings with cowpox but not from animals. He then asks his sister whether there is any danger of transmitting something from the cow to the children besides the cowpox. In a subsequent letter Claudius states that he is glad to learn that his grandchildren have been successfully vaccinated with cowpox.

BRAHDY, Mount Vernon, N. Y.

EPIDEMIC ACUTE POLIOMYELITIS AND ENCEPHALITIS, BOTH AIR-BORNE INFECTIONS. W. S. BRYANT, Acta pædiat. **19**:392, 1937.

This is a cursory summary of some of the experimental and clinical aspects of epidemic encephalitis and of acute anterior poliomyelitis. It is useful because of its content of bibliographic material, but it contains no new observations or account of original work which has not been previously published elsewhere. The author takes advantage of the occasion to reiterate his conviction that immunity against poliomyelitis is conditioned to an important degree by anatomic and functional peculiarities of the nasopharynx; these vary with the age of human subjects.

MCCUNE, New York.

Acute Infectious Diseases

STUDIES ON OXYURIASIS COLON. I. TYPES OF ANAL SWABS AND SCRAPERS, WITH A DESCRIPTION OF AN IMPROVED TYPE OF SWAB. M. C. HALL, Am. J. Trop. Med. **17**:445 (May) 1937.

Hall studied various types of anal swabs and scrapers to determine the most satisfactory kind to use in detecting the ova of pinworms. After experimenting with various swabs he devised an anal swab known as the NIH swab, which consists of a glass rod inserted into a perforated cork, the tip of the rod being covered with a small square of cellophane. This is inserted into a test tube until used. With this swab, which acts both as a swab and a scraper, he claims to have had much better results in diagnosing pinworms than with any previously devised ones.

BURPEE, Augusta, Ga.

RELATION OF FUNGUS INFECTION OF GRAIN CROPS TO VASOMOTOR DISTURBANCES IN MAN. J. E. KLEIN, Ann. Int. Med. **10**:1708 (May) 1937.

Klein states that common cereals are frequently subject to fungus infection and that the ingestion of such food over a period of years may be the cause of such disturbances as acrodynia, Buerger's disease, erythromelalgia, Raynaud's disease and acroparesthesia.

READING, Galveston, Texas.

THE CLINICAL USES OF HUMAN SERUMS PRESERVED BY THE LYOPHILE PROCESS. A. C. MCGUINESS, J. STOKES JR. and S. MUDD, J. Clin. Investigation **16**:185 (March) 1937.

This paper describes the use of human serums, preserved by the lyophile process, from large pools of normal healthy adult blood, in the prophylaxis of the more common contagious diseases and the treatment of scarlet fever, mumps, erysipelas, whooping cough and acute infections due to hemolytic streptococci. The results compared favorably with those reported by other investigators who have employed fresh serums preserved in the liquid state. Distinctive advantages of lyophile serums are indicated and illustrated with case material.

GUEST, Cincinnati.

A Case of Rat-Bite Fever with Demonstration of Spirillum Minus. O. Bloch Jr. and H. Baldock, J. Pediat. **10**:358 (March) 1937.

A case of rat-bite fever in a 3 year old girl is reported. The diagnosis was definitely established by the presence of Spirillum minus in the blood of two mice which twenty days previously had been given an injection intraperitoneally of 2 cc. of venous blood taken from the patient at the height of the fever. The spirilla were found in dark field preparations. Often the spirilla did not appear for the first hour after the drop of blood had been placed on the slide; later they could be seen shooting to and fro in the spaces among the red blood cells. Other moving bodies were seen in the preparations which might cause confusion in diagnosis. The first was a motile bacterium which appeared after the preparation had stood for from one to two hours. The second was a fine, wavy, scintillant filament, attached to the red cells and fluttering in currents of plasma. The third was a small, refractile, rapidly moving particle seen inside the red cells, especially if hemolysis was present. Another source of error, not present in this case, is the occasional presence of spirilla in the blood of the mouse before inoculation. Control examination of the mouse's blood before inoculation is advisable.

Rauh, Cincinnati.

Protective Antibodies in the Blood Serum of Individuals After Immunization with Typhoid Vaccine. J. F. Siler and others, Mil. Surgeon **80**:91 (Feb.) 1937.

The findings in virulence tests, cross-immunity experiments in mice and mouse protection tests reported in this and a previous communication suggest strongly that there are two important criteria to be followed in the selection of a strain of the typhoid organism for the preparation of vaccine for immunization against typhoid fever: (*a*) The strain of the organism should be highly virulent. (*b*) The strain should be highly immunogenic as demonstrated by active and passive immunity tests in a selected breed of mice.

Sanford, Chicago.

Active Immunization Against Tetanus with Tetanus Toxoid. W. W. Hall, Mil. Surgeon **80**:104 (Feb.) 1937.

These results were obtained by titration of the blood of 140 army volunteers. Satisfactory immunity may be obtained with tetanus toxoid. Alum-precipitated tetanus toxoid is a much more potent antigen than unrefined toxoid. It is remarkably thermostabile. Intervals of from six to eight weeks between injections are more effective than shorter intervals. Reactions are negligible, consisting of local induration, slight general malaise and slight elevation of temperature. When the injections are given intramuscularly, induration lasts forty-eight hours; when they are given subcutaneously, it lasts longer. Two urticarial reactions were noted with plain toxoid; none, with alum-precipitated toxoid. Secondary stimulation at a long interval after the primary stimulation is effective in quickly raising the immunity to a high level. No one in the series was found to be refractory to toxoid immunization. It is believed, therefore, that immunization against tetanus by injection of toxoid could advantageously be substituted for the use of tetanus antitoxin in certain selected groups.

Sanford, Chicago.

The Treatment of Acute Rheumatism in Childhood. R. Lightwood, Lancet **1**:613 (March 13) 1937.

In view of the recognition of the three phases of acute rheumatism—infection of the throat, a latent period and the rheumatic attack—it is the clinician's duty to make practical use of this knowledge. The first problem is to prevent infection of the throat in rheumatic children. To this end sufficient rooms for isolation should be provided so that every patient with tonsillitis among rheumatic children can be separated from the other patients.

As far as treatment of tonsillitis and pharyngitis is concerned, Lightwood places chief reliance on painting the tonsils with a solution of strong protein silver and giving potassium chlorate by mouth. Activity should not be resumed until the pulse rate and the sedimentation rate are normal.

Clinical experience suggests that a complete tonsillectomy lessens the number of infections of the throat and may, therefore, be expected to be a help in suitably picked cases. "Certainly we ought not to advise the removal of normal tonsils from any child, even a rheumatic one."

Every patient showing any evidence of rheumatic activity is nursed almost flat with but one pillow, is allowed no active movement except of the hands, and is fed by a nurse so that the work of the heart is reduced to a minimum. When all signs of rheumatic activity have passed, a gradual return to ordinary life is permitted.

Acetylsalicylic acid has not yet been proved clinically to be of definite prophylactic value in the silent period. Of the many drugs that have been used with the object of checking the rheumatic infection, none is of primary importance.

LANGMANN, New York.

WEIL'S DISEASE IN BRISBANE. D. W. JOHNSON, H. E. BROWN and E. H. DERRICK, M. J. Australia **1**:811 (May 29) 1937.

The authors report three cases of classic Weil's disease occurring in Brisbane. Two of the patients were sewer workers. In a series of 85 wild rats examined in Brisbane in 1936, 2 were found to be carriers of leptospirae; in a second series of 100 rats examined in March 1937, 6 were found to be carriers of leptospirae. This is the first time that cases of classic Weil's disease and the specific type of Leptospira have been recorded in Australia. The carrier rate, however, being comparatively low, Weil's disease may be expected to occur only sporadically.

GONCE, Madison, Wis.

UNDULANT FEVER. C. HARDWICK, Proc. Roy. Soc. Med. **30**:880 (Feb.) 1937.

A patient aged 5 years was admitted to the hospital in February 1937 with a history of sudden onset of pyrexia in January; the fever lasted for fourteen days. The temperature would be normal in the morning and would rise to 102 F. at night. On examination no abnormal signs were found except that the spleen was enlarged to about 2 fingerbreadths below the costal margin. The temperature remained normal while the child was in the hospital. The sedimentation rate (micromethod) was 9 mm. in the first hour. The Mantoux and Wassermann reactions were negative. Agglutination of Brucella abortus was positive up to a titer of 1:1,000; there was slight agglutination of Brucella melitensis.

WILLIAMSON, New Orleans.

HEPATIC TYPE OF TYPHOID FEVER IN CHILDREN. E. CASSOUTE and M. H. KHANH, Arch. de méd. d. enf. **40**:101 (Feb.) 1937.

During the period from July 1, 1935, to Nov. 1, 1936, there were 105 cases of typhoid fever among children admitted to the University Hospital at Marseilles, 12 of which terminated in death. Autopsies were secured in 5 cases. The complications encountered were intestinal perforation with hepatonephritis (2 cases), hepatitis with intestinal hemorrhage (1 case) and hepatitis alone (2 cases). Complete clinical histories of these children are included in the report. In at least 3 of the cases in which autopsy could not be secured there was evidence of grave hepatic insufficiency, which leads the authors to assume that typhoid involves the liver more commonly than authorities would have one believe.

AMESSE, Denver.

A Neurovegetative Disturbance in Acute Rheumatic Arthritis. Warembourg and Laine, Gaz. d. hôp. **110**:685 (May 26) 1937.

This is a report of a case of rheumatic fever in which involvement of the vegetative nervous system dominated the picture from the very beginning. Besides rapid failure of the heart, the salient symptoms were transient erythema, cyanosis which could not be explained by the condition of the heart, attacks of profuse sweating associated with copious bronchial and nasal secretion containing numerous eosinophil leukocytes, angioneurotic edema and Raynaud's disease leading to gangrene of the fingers, and cerebral edema before death. Kajdi, Baltimore.

Parotitis During Typhoid. M. Battista, Med. inf. **8**:83 (March) 1937.

In a child of 5 during a relapse of typhoid parotitis involving only the left side developed. Pus could be expressed from Stensen's duct. Treatment was by medical means and resulted in cure. The bacteria present in the pus expressed from the duct were not determined.

Reports from other authors indicate that both typhoid bacilli and organisms from the buccal flora are observed in cases of parotitis associated with typhoid. There is a disagreement as to whether the infection is hematogenous in origin or occurs by extension through the parotid ducts. In most cases only one parotid gland is involved; in rare cases the parotitis has been present bilaterally.

Higgins, Boston.

Considerations and Investigations on the Occurrence of Brucelliasis in Infancy. U. Di Aichelburg and G. Prandi, Arch. ital. di pediat. **5**:115 (April) 1937.

Among 5,253 children admitted to the pediatric clinic of the University of Turin between January 1926 and September 1936, there were 6 whose illness was diagnosed as brucelliasis, the diagnosis being confirmed by positive blood serum agglutination tests. None of the group was under 2 years of age. A group of 155 children between 2 and 12 years of age was studied for the presence of agglutinins. Five of these had positive reactions. One of the later group of positive reactors had pulmonary tuberculosis; one, acute adenoiditis; one, bronchopneumonia; one, a febrile illness which may have been brucelliasis, and one was apparently quite healthy. Children are brought to this clinic not only from the city of Turin but also from the whole of the rural region of Piedmont. Dooley, New York.

The Phagocytic Function of the Reticulo-Endothelial System in Visceral Leishmaniasis of Children as Demonstrated by the Congo Red Test. F. Paradiso and G. Ernandez, Lattante **8**:348 (May) 1937.

The ability of the reticulo-endothelial system to absorb a colloid such as congo red is the basis of the functional test of Adler and Reimann. A solution of congo red is injected intravenously; four minutes later a specimen of blood is withdrawn; another specimen is withdrawn one hour later. The serums of the two specimens are compared for color (congo red content), and the percentage of the dye not absorbed in one hour is determined. Normally between 50 and 70 per cent of the dye has not been absorbed. A low absorption of dye by the reticulo-endothelial system indicates poor function.

Observations were made before and after treatment of eight children with leishmaniasis. The congo red retention in the blood was above normal in seven before treatment; in three it fell to normal after treatment; in the other four it fell after treatment, but not to normal. In one child the retention was normal before and rose after treatment; this child had not responded well to treatment.

Higgins, Boston.

DYSENTERIC SYNDROMES OF INFANCY AND CHILDHOOD. R. ODRIOZOLA, Arch. de pediat. d. Uruguay **8**:65 (Feb.) 1937.

From a large series of cases Odriozola concludes that in Paraguay the dysenteric syndrome may be produced by various infectious agents. He presents seventy-one cases of dysentery caused by different forms of dysentery bacilli (in twenty of these the bacilli were of the Shiga type), thirteen due to Endamoeba histolytica, ten associated with helminthiasis, five associated with other protozoa (Giardia in some) and twenty-two secondary to influenza. The symptoms were practically the same in many cases from different groups.

He also gives a brief discussion on the epidemiology of dysentery in his country in the past seventy-five years and stresses the fact that recently the mortality has been very low (below 15 per cent). In the aforementioned series of cases there were only eight deaths in the bacillary group and one in the ameba group.

The treatment in these cases varied with the etiology. In addition to symptomatic therapy he used dysentery serum or bacteriophage in the treatment of Bacillary dysentery and chiniofon in the treatment of the amebic forms.

SCHLUTZ, Chicago.

RABIES MENINGITIS. J. BONABA, J. J. L. SIRI and C. F. MUNOZ, Arch. de pediat. d. Uruguay **8**:91 (Feb.) 1937.

An 8 year old girl was bitten by a rabid dog (proved to have rabies by examination). Subsequent to this she received an intense course of Pasteur's treatment for twelve days, and then meningitis developed. The spinal fluid showed 416 cells per cubic millimeter the majority of which were polymorphonuclears, with a complete absence of organisms (bacteria) in smear and culture. The child died on the third day of the disease, and necropsy showed meningo-encephalitis. A suspension of spinal cord from the patient when injected into rabbits produced demonstrable rabies. The authors conclude that the condition was due to street virus.

SCHLUTZ, Chicago.

BANANA DIET IN INFANTILE DYSENTERY. O. T. DÁ MATTA, J. de pediat., Rio de Janeiro **4**:118 (March) 1937.

From his experience with four infants with diarrhea dá Matta believes that this treatment is excellent.

SANFORD, Chicago.

TYPHOID ENCEPHALITIS: DIFFERENTIATION FROM INFECTIOUS ENCEPHALOMENINGITIS. H. G. HUBER, Kinderärztl. Praxis **8**:152 (April) 1937.

This is a description of the case of a girl 11 years of age who presented all the symptoms characteristic of encephalitis. The spinal fluid was normal; the temperature, 38.5 C. (101.3 F.); tuberculin reactions were negative. Leukopenia (4,400 white blood cells), a positive Widal reaction and the observation that two siblings became ill from two to three weeks later with typical typhoid infection left no doubt as to the diagnosis of typhoid encephalitis in the case described.

HEYMANN, Cleveland.

STAPHYLOCOCCUS TOXOID AS A MODE OF TREATMENT. W. A. TIMMERMAN, Nederl. tijdschr. v. geneesk. **81**:1725 (April 17) 1937.

A number of patients suffering from various conditions caused by staphylococci were treated with staphylococcus toxoid. There were favorable results in recurrent furunculosis; in various forms of acne the results were dubious. The initial dose should be small, and the dose should be increased slowly, with close observation of the reactions caused by the injections. Pyrexia and recrudescence of symptoms indicate that the dose has been too large.

VAN CREVELD, Amsterdam, Netherlands.

PARATYPHOID A IN THE NETHERLANDS. A. W. POT, Nederl. tijdschr. v. geneesk. **81**:2339 (May 22) 1937.

Pot offers a survey of the occurrence of paratyphoid A in Holland with a communication concerning a case observed at Wageningen in September 1936. The disease is very rare in Holland. VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

PREVENTION OF CONGENITAL SYPHILIS. G. F. HOGAN, New York State J. Med. **37**:929 (May 15) 1937.

With a total of 1,179 pregnancies in 336 women, adequate syphilitic treatment was given in 102 pregnancies. Seven of the children in cases in which treatment was adequate gave evidence of congenital syphilis. In the 1,077 cases in which treatment was inadequate congenital syphilis was noted in 442 children.

AIKMAN, Rochester, N. Y.

CHILDHOOD TYPE TUBERCULOSIS. W. B. GRAYSON and W. MYERS SMITH, South. M. J. **30**:400 (April) 1937.

Grayson and Smith outline the difference between the childhood and the adult type of tuberculosis on the basis of age incidence, sex incidence, prognosis, complications and source of infection. They summarize the results of recent investigations on the rôle of immunity and allergy in resistance to tuberculosis. They point out that the most recent statistics show increasing value in the application of tuberculin tests to adults. Hence, a public health program for the control of tuberculosis should include wide-spread tbuerculin tests. Facilities for interpreting such tests and for obtaining good roentgenograms are necessary.

An important preventive and also corrective measure is the hospitalization of adults. After breaking the contact in this way, public health education in the home will suffice for most of the children with tuberculosis. SCHLUTZ, Chicago.

TUBERCULOSIS IN WILD VOLES. A. Q. WELLS, Lancet **1**:1221 (May 22) 1937.

The field or meadow vole (Microtus agrestis), widely known as the short-tailed field mouse or grass mouse (though it is not a mouse) is very numerous in the meadows of the British Isles. It has been observed for many years that this mammal is subject to wide fluctuation in numbers.

Since February of this year Wells has found 134 voles with lesions of tuberculosis. These lesions contained acid-fast bacilli resembling tubercle bacilli. Whether these bacteria are pathogenic in other animals or man has not been determined. LANGMANN, New York.

ACTINOMYCOSIS OF THE LUNG. S. CAMPBELL and A. J. HARDY, Proc. Roy. Soc. Med. **30**:876 (Feb.) 1937.

This condition was reported in a girl of 9 years. In June 1935 the mother noticed a small firm lump, slightly tender, a few inches below and lateral to the nipple line. There was a short dry cough. The swelling was opened, and the pus obtained showed the gram-positive branching mycelia of actinomycosis. She was given large doses of potassium iodide and local roentgen treatment. She was placed in a convalescent home until February 1937, when she returned to the hospital, where numerous sinuses over the right lower region of the thorax and also over the lumbar region were found. Physical signs of fibrosis were present in the right lower part of the thorax, together with signs of an enlargement of the heart. Roentgen examination showed thickened pleura and fibrosis of the lower lobe of the right lung. The heart and mediastinum were displaced to the right. The child was given injections of increasing amounts of mixed actinomycotic vaccine and roentgen radiation to the affected parts.

WILLIAMSON, New Orleans.

TUBERCULOSIS OF INFANCY. P. RUEDA, Arch. de méd. d. enf. **40**:222 (April) 1937.

As knowledge of the natural history of tuberculosis develops, the hope of developing means for its prevention grows stronger. The belief that this infection is rarely found in very young persons was first combated by the author, who also disputed the dictum, accepted until recently, that juvenile infections were closed processes and therefore incapable of conveying the disease to contacts. Examination of gastric contents shows that from 80 to 90 per cent of patients with active disease eliminate the Koch bacillus in more or less virulent form.

Another opinion which seemed fairly fixed but which has been demonstrated as entirely false is that the prognosis in tuberculous nurslings is universally poor. The pendulum has now swung so far in the opposite direction that there is some danger of open neglect in the assumption that these patients are spontaneously cured. The views of the older writers that tuberculosis is hereditary and is essentially incurable are unfortunately still accepted in lay circles. The practical deductions to be made from this increase in knowledge are obvious. False doctrines must be eradicated, and marriage during the active stage must be prevented. To prevent extension of the individual infection, Rueda suggests that in all subjects suffering from tuberculosis of the respiratory tract, especially those with abundant secretion, gastric lavage should be practiced at regular intervals. While this would be practicable among adults, it would not be easy with infants; he therefore suggests that a few drops of syrup of ipecac be administered and the resulting vomitus examined for bacilli. In the prevention of autoinfection, minute doses of apomorphine, given subcutaneously, are also recommended, but only in those cases in which there is no response to such emetics as ipecac.

AMESSE, Denver.

ASSISTANCE TO CHILDREN OF TUBERCULOUS PARENTS. P. BRUSA, Lattante **8**:281 (May) 1937.

Brusa discusses the social and medical care which should be given to infants of tuberculous mothers.

HIGGINS, Boston.

BILATERAL PNEUMOTHORAX IN PULMONARY TUBERCULOSIS IN EARLY CHILDHOOD. S. BARBERI, Lattante **8**:303 (May) 1937.

A child of 2 years had tuberculous infiltration of both lungs and foci of bronchopneumonia in the right lung. Puncture of a lung yielded tubercle bacilli. A therapeutic pneumothorax was done on the left side and a short while later on the right. The clinical results were excellent, and the child was discharged completely cured three years later.

HIGGINS, Boston.

PROPHYLAXIS AGAINST TUBERCULOSIS IN CHILDREN. M. BERGAMINI, Lattante **8**:363 (May) 1937.

Prophylaxis against tuberculosis is of two types: "prophylaxis of disposition" and "prophylaxis of exposition." The first type is concerned with eugenics, with building up general body resistance, with proper hygiene and diet and with protection against secondary infections. The second type involves early diagnosis, preventive inoculations and sanatorium care. Bergamini pleads for a uniform national program dealing with tuberculosis in Italian children.

HIGGINS, Boston.

SPEED OF SEDIMENTATION OF RED CELLS IN PATIENTS WITH TRACHEOBRONCHIAL ADENOPATHY DURING A SOJOURN AT THE SEASHORE. G. SANPAOLESI, Riv. di clin. pediat. **35**:420 (May) 1937.

At the seaside hospital in Viareggio observations were made on the sedimentation rates of 21 normal children and 100 children with tracheobronchial adenitis.

Whereas 57 of the latter showed abnormal sedimentation rates at the beginning of the observations, after from two to four months' treatment only 20 had rates that were abnormal. The sedimentation rate afforded a good index as to the state of the tuberculous infection.

HIGGINS, Boston.

PERITONEAL TUBERCULOSIS. FRANCISCO LAPORT and OSWALDO PINHEIRO CAMPOS, Arch. de pediat., Rio de Janeiro **9**:197 (April) 1937.

According to Laport and Campos three forms of peritoneal tuberculosis are found: an active localized form, in which surgical therapy is the only hope; an active generalized form, which is not amenable to treatment, sedatives perhaps being necessary to keep the patient comfortable, and a chronic form, which does not require surgical treatment. A patient affected with the last type may recover if hygiene and diet are adhered to and heliotherapy and actinotherapy are used as adjuvants.

SANFORD, Chicago.

THE ORIGIN OF JUVENILE PULMONARY TUBERCULOSIS. WALTER SCHWENK, Monatschr. f. Kinderh. **70**:9 (April) 1937.

This is a comprehensive article on juvenile pulmonary tuberculosis and is illustrated with serial roentgenograms of children with this condition who were followed over a number of years. Schwenk believes that his evidence shows that progressive pulmonary tuberculosis in children can have its origin in the apexes of the lungs. All of his patients were girls. He thinks that this is due to the earlier onset of puberty in girls, puberty predisposing to the spread of the disease. In eight of his ten patients the onset of the disease occurred between the tenth and the fourteenth year; in one it occurred at 8 years of age and in another at 6. The development into open pulmonary tuberculosis in nine patients became manifest between the twelfth and the eighteenth year. Puberty apparently is a dangerous period. Schwenk found the condition to be uninfluenced by treatment in his cases. Whether the spread of the disease really came from the focus in the apex, he is not absolutely certain. In five cases there was a history of subsequent exposure. In the remaining five there was nothing indicative of a subsequent infection.

GERSTLEY, Chicago.

TUBERCULOUS MENINGITIS. D. VON MORITZ and T. MESZNER, Monatschr. f. Kinderh. **70**:232 (May) 1937.

The writers demonstrate hypochloremia in patients with tuberculous meningitis. This may be due to loss of salt through vomiting or perspiration. It may also be due to dilution of the blood, as there seems to be some retention of water in this condition. There is no increase in the excretion of sodium chloride through the kidneys.

GERSTLEY, Chicago.

Diseases of Blood, Heart and Blood Vessels and Spleen

THE DIPHASIC QRS TYPE OF ELECTROCARDIOGRAM IN CONGENITAL HEART DISEASE. L. N. KATZ and H. WACHTEL, Am. Heart J. **13**: 202 (Feb.) 1937.

Electrocardiograms of 43 cases of congenital heart disease were analyzed with particular reference to a diphasic QRS (with the size of the two phases being of the order of less than 1 to 4). There were 56 instances of diphasic QRS out of a possible total of 129: 26 in lead I, 14 in lead II and 16 in lead III. The presence of such a diphasic QRS is confirmatory of the diagnosis of congenital heart disease, and when the two phases are large and of equal extent the finding is pathognomonic.

GIBSON, Chicago.

STUDIES OF BLOOD FORMATION IN THE FETUS AND NEWBORN. M. M. WINTROBE, ROY E. KINSEY, RANKIN C. BLOUNT and WILLIAM TRAGER, Am. J. M. Sc. **193**:449 (April) 1937.

The gastric function in the fetus and the new-born infant is discussed. Although anatomic development is incomplete at birth, it is possible that physiologic activity may commence before this time. The administration of liver extract to pregnant animals and its injection into the placenta appeared to have no effect on the blood of rabbit fetuses. No antianemic potency was found in fetal liver extracts or in placental extracts. The growth factor needed by mosquito larvae, which is found in high concentration in extract of adult liver, was present in very small quantities in extracts of placenta and in somewhat greater amounts in fetal liver extracts. The observations recorded are consistent with the hypothesis that the antianemic principle of Castle may play a rôle in fetal hematopoiesis, but afford no direct proof of such a relationship.

HENSKE, Omaha.

PHYSIOLOGICAL AND NUTRITIONAL ANEMIAS OF INFANCY. G. R. ALPERT, Arch. Pediat. **54**:268 (May) 1937.

A comprehensive review of the subject is presented. Physiologic anemia develops in all infants, premature and full term alike. It is most pronounced at the second to third months of life. Prophylaxis of physiologic anemia should be a routine procedure for all infants. The results are more striking in full term infants. Iron in a soluble form is the best therapeutic agent, with the exception of blood given parenterally. Ferric pyrophosphate is offered as a suitable iron compound.

The use of copper in the treatment of anemia is still unsettled, though copper as a supplement to iron should receive a longer period of clinical trial. Iron with liver may be of value as a therapeutic agent.

ORR, Buffalo

CONSERVATION OF BLOOD IRON DURING THE PERIOD OF PHYSIOLOGICAL HEMOGLOBIN DESTRUCTION IN EARLY INFANCY. G. STEARNS and J. B. MCKINLEY, J. Nutrition **13**:143 (Feb.) 1937.

The investigation proposes to determine the fate of the iron freed by the breakdown of hemoglobin during the early weeks of life. This is important, as it is believed that the amount of iron freed in early infancy greatly exceeds the amount in storage at the time of birth.

The excretion of iron of seven infants was studied during the destruction of blood. In addition, seventeen other infants under 3 months of age were used in certain observations on alterations in cell volume, erythrocytes, hemoglobin and blood iron.

It was found that the iron in the blood reached its minimal volume between the fourth and sixth weeks of life and that the excretion of iron of each infant studied during the period of decreasing blood was always greater than the intake. The loss of iron from the body continued for some time after the iron in the blood had reached a minimum. The average daily loss was 1.25 mg., and the estimated total loss for the period was from 50 to 75 mg. One premature infant showed as great a loss of iron from the body as did the full term infants. No infant was able to conserve all the iron from the excess of hemoglobin.

The authors conclude that a dietary source of iron is desirable well before 6 months of age.

MUNNS, Winnetka, Ill.

ATRESIA OF THE PULMONARY ORIFICE WITH INTACT INTERVENTRICULAR SEPTUM. M. M. STEINER, J. Pediat. **10**:370 (March) 1937.

Steiner reports a case of atresia of the pulmonary orifice with an intact interventricular septum in a still-born Negro male infant. In addition bilateral hydronephrosis, umbilical hernia and absence of the auricles, with atresia of the external auditory canals, were present. This cardiac anomaly is very rare. Among eight hundred and fifty cases of congenital cardiac abnormalities Abbott listed only seven such instances.

RAUH, Cincinnati.

THE IRON-DEFICIENCY ANAEMIA OF LATE INFANCY. H. W. FULLERTON, Arch. Dis. Childhood **12**:91 (April) 1937.

Hemoglobin levels were subnormal—less than 80 per cent (Haldane)—in 87 per cent of 298 infants between the ages of 9 and 23 months belonging to the poorer classes. The common anemia of late infancy is due mainly to deficiency of iron, which is dependent on low weight at birth, artificial feeding and infective illnesses. Probably infections have the additional effect of inhibiting the formation of blood. Anemia in infancy depends only to a slight extent, if at all, on the ordinary maternal deficiency of iron. The incidence of anemia among infants of the better classes is probably somewhat less than that among the poor.

KELLY, Milwaukee.

GASTRIC ACIDITY IN INFANTS AND YOUNG CHILDREN UNDER NORMAL AND PATHOLOGICAL CONDITIONS, WITH SPECIAL REFERENCE TO NUTRITIONAL ANEMIA. A. STEWART, Brit. J. Child. Dis. **34**:1 (Jan.-March) 1937.

Stewart found no evidence that congenital failure of gastric secretion was responsible for the development of the simple iron deficiency or nutritional anemias of infancy. It would appear extremely probable that the impairment of gastric secretion is the result rather than the cause of the anemia.

The low acidity decreases still further the amount of available iron, thus aggravating the condition and preventing spontaneous cure.

It is probable that infective states, particularly enteritis, play a part in the etiology of the nutritional anemias of childhood by causing chronic gastritis, with suppression of acid secretion, as suggested by Faber, but this point requires further investigation.

LANGMANN, New York.

HÆMOPHILIA AND COLOR BLINDNESS OCCURRING IN THE SAME FAMILY. W. J. B. RIDDELL, Brit. J. Ophth. **21**:113 (March) 1937.

The pedigrees of seven hemophilic families were investigated as far as practicable, and the affected members were examined for color defects. Ishihara's isochromatic plates were used in all cases, but additional tests were used for confirmation. Only one pedigree of a family which showed color blindness associated with undoubted hemophilia was obtained, and this was secured from a dental clinic. The relevant portion of this pedigree is shown in the diagram.

ZENTMAYER, Philadelphia. [ARCH. OPHTH.]

DISCUSSION ON THE COURSE AND MANAGEMENT OF CONGENITAL HEART DISEASE. C. B. PERRY, Proc. Roy. Soc. Med. **30**:693 (April) 1937.

The discussion is limited to those types of congenital cardiac defect which are compatible with life and are recognizable clinically. The author takes Maude Abbott's classification of congenital heart disease, which has given a valuable working conception of the condition. She divides the cases into two large groups, those with cyanosis and those without. Perry discusses both types and then sums the matter up as follows: The prognosis in acyanotic types of congenital heart disease is good. The patients should live normal lives and should take care

to avoid superimposed bacterial infection. Patients with cyanotic heart disease should lead restricted lives. The degree of restriction and the prognosis depend almost entirely on the severity of the cyanosis and other symptoms. Drs. T. East, D. C. Muir, J. W. Brown, A. G. Gibson and Evan Bedford took part in the discussion.

WILLIAMSON, New Orleans.

CIRSOID ANEURISM INVOLVING TONGUE AND FLOOR OF MOUTH. C. E. HENDERSLEY, Proc. Roy Soc. Med. **30**:709 (April) 1937.

A case in a girl of 12 years is reported. Hendersley first gives the surgical treatments which he has tried without obtaining any improvement, then states that he presents the case to the society for suggestions as to treatment.

WILLIAMSON, New Orleans.

SPLENOMEGALY WITH LIPAEMIA. S. M. FRANKLIN, Proc. Roy. Soc. Med. **30**:711 (April) 1937

A girl of 5 years suffered frequent infections of the respiratory tract. The spleen was first noticed to be enlarged at the age of 7 months. On admission of the child to the hospital the organ was found to be 2½ inches (6 cm.) below the costal margin. The patient was below the average weight and height for her age. Her blood after withdrawal separated at once into an upper creamy layer and a lower jellylike clot. The upper again separated into a clear colorless portion and a supernatant cream. Examination of splenic pulp showed, scattered all over the film, minute patches of scarlet red-positive material, extracellular. This was not present in films made from capillary blood.

Further investigations are given in the report.

WILLIAMSON, New Orleans.

SESAME OIL AND THROMBOCYTES. K. BATTEREAU, Monatschr. f. Kinderh. **69**:389 (March) 1937.

In seven cases Battereau could not confirm the findings of Schiff and of Schiff and Hirschberger that small doses of oil of sesame increase the thrombocyte count.

GERSTLEY, Chicago.

A CASE OF COR TRILOCULARE BIATRIATUM WITH HYDROCEPHALUS. S. VAN CREVELD, Maandschr. v. kindergeneesk. **6**:221 (March) 1937.

A description is given of a case of cor triloculare biatriatum, together with a discussion of some of the peculiarities of this case, for instance, the development of hydrocephalus. Further report is made of a case of congenital heart failure which gave rise to a neurologic complication and a case of dislocation of the heart, combined with a neurologic complication.

VAN CREVELD, Amsterdam, Netherlands.

IDIOPATHIC HYPERTROPHY OF THE HEART: CARDIOMEGALIA CONGENITA IN RELATION TO GLYCOGEN DISEASE. B. L. MUTGEERT, Maandschr. v. kindergeneesk. **6**:233 (March) 1937.

The author observed two cases of idiopathic hypertrophy of the heart. In the first one, in which no study could be made before death, the hypertrophy proved to be caused by an accumulation of glycogen. In the second case, in which the carbohydrate metabolism was especially studied during life, no explanation of the hypertrophy was revealed at autopsy. The name idiopathic hypertrophy must be reserved to make a distinction from glycogenic cardiomegalia (Pompe).

VAN CREVELD, Amsterdam, Netherlands.

IDIOPATHIC HYPERTROPHY OF THE HEART: DIFFUSE RHABDOMYOMATOSIS AND GLYCOGEN DISEASE. B. J. MANSENS, Maandschr. v. kindergeneesk. **6**:246 (March) 1937.

The author gives a report of the histologic examination of the heart in the two cases of cardiac hypertrophy described by Mutgeert (*Maandschr. v. Kindergeneesk.* **6**:231 [March] 1937). The glycogen content of the heart in the first case was 10 per cent; that in the second case, 1.3 per cent.

VAN CREVELD, Amsterdam, Netherlands.

POLYPEPTIDEMIA. E. GORTER, Maandschr. v. kindergeneesk. **6**:270 (April) 1937.

In several morbid pictures characterized by the occurrence of toxic symptoms, the following chemical deviations are found to be present in the blood: hyperazotemia, hypochloremia and hyperpolypeptidemia. The significance of the polypeptidemia for the occurrence of the toxic symptoms was studied. Experimentally it was found that intestinal occlusion caused an increase of the polypeptides, of the proteolytic ferments and of the potassium in the blood. In some morbid conditions in children analogous results have been obtained, e. g., in cases of uremia. According to Gorter, the physicotoxic activity of the polypeptides greatly influences their toxic properties; the polypeptides may diminish the solubility of the proteins in the blood.

VAN CREVELD, Amsterdam, Netherlands.

BLOOD PICTURE, SEDIMENTATION RATE AND COAGULATION TEST OF WELTMANN. B. J. W. BEUNDERS, Nederl. tijdschr. v. geneesk. **81**:1538 (April 10) 1937.

A number of cases are recorded in which valuable help in the establishment of the diagnosis has been given by the combination of the Weltmann coagulation test, the sedimentation rate of the blood and the morphologic blood picture. The Weltmann test is of special value for the detection of exudative processes and is mainly useful for the differentiation between inflammatory processes and neoplasms and in such conditions as the adnexitis of ectopic pregnancy. Valuable data have also been obtained by the Weltmann test in combination with the sedimentation rate and the blood picture in the control of tuberculous processes. In inflammatory processes coagulation of protein occurs in dilutions of 0.7 : 1,000 or higher concentrations (in dilutions of up to over 1 : 1,000), and in conditions with intense formation of fibrous tissue (e. g., cirrhosis of the liver) in dilutions of from 0.1 : 1,000 to 0.2 : 1,000; the normal coagulation point is 0.4 : 1,000. In cases of neoplasms and in ectopic gestation the coagulation does not depart from the normal; the sedimentation rate is generally raised in cases of neoplasms.

VAN CREVELD, Amsterdam, Netherlands.

DETECTION OF ERYTHROCYTES OF THE DONOR AFTER BLOOD TRANSFUSION BY MEANS OF ANTI-M AND ANTI-N TEST FLUIDS. L. VAN DER SPEK and H. J. N. DEKKERS, Nederl. tijdschr. v. geneesk. **81**:1552 (April 10) 1937.

A method is described for the detection of erythrocytes of the donor in the blood of the receptor, by means of anti-M and anti-N test fluids (Landsteiner). The heterologous corpuscles are demonstrated by their direct agglutination by specific hetero-agglutinins. This will be possible only if the erythrocytes of the donor and those of the receptor belong to different blood groups with regard to the M and N factors and if the erythrocytes of the receptor contain only one of these factors. In this way one can determine the time during which the corpuscles of the donor remain detectable in the receptor's circulation. In two cases here described the authors could demonstrate the transfused blood corpuscles even forty-one and sixty-five days after the transfusion.

VAN CREVELD, Amsterdam, Netherlands.

DURATION OF LIFE OF ERYTHROCYTES BEFORE AND AFTER TREATMENT OF PERNICIOUS ANEMIA BY MEANS OF LIVER. L. S. ORNSTEIN and J. F. SCHOUTEN, Nederl. tijdschr. v. geneesk. **81**:1717 (April 17) 1937.

It appeared to be possible to establish a simple relation between the remarkable changes taking place in the concentration of bilirubin in the blood serum of patients with pernicious anemia during treatment with liver and the laws governing the death rate of red blood cells in relation to their age before and after this treatment. The difference between the two types is twofold: First, the mean age before the treatment varies between nine and nineteen days, whereas after the treatment it varies between thirty-seven and ninety days. Second, the rate of mortality is of a different type before and after treatment. The "anomalous" cells have a mortality practically independent of their age, whereas the mortality of the "normal" cells is highly dependent on their age. The anomalous cells thus die at random and the normal cells at an age not differing much from the mean age.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Nose, Throat and Ear

THE HAIMAN CORRELATION OF VASOMOTOR SYMPTOMS ASSOCIATED WITH NASAL MANIFESTATIONS IN CHILDREN. J. A. HAIMAN, Arch. Pediat. **54**:236 (April) 1937.

Haiman lists a group of apparently unrelated symptoms which he claims are associated and constitute a vasomotor syndrome. He also states that the syndrome is clearly defined and that if one will follow the various symptoms mentioned, the diagnostic features will present themselves vividly.

The following symptoms are mentioned: swollen nasal mucosa, cough, postnasal drip, frequent colds, sneezing, lacrimation of the eyes, lack of tonicity, late afternoon fatigue, emotional, high strung, tense gastro-intestinal manifestations, vomiting, pain simulating appendicitis, skin manifestations, vesicular rashes, urticarial phenomena, cardiac manifestations, tachycardia.

These symptoms will be found in cases of vasomotor rhinitis and nasal sinusitis, cases of croup and tracheobronchitis and very occasionally cases of hay fever and asthma.

ORR, Buffalo.

FOREIGN BODIES IN THE EAR AND THEIR REMOVAL. E. H. GRIFFIN, M. Rec. **145**:409 (May) 1937.

Griffin reports a few cases of foreign body in the ear and states that such bodies are best removed by use of a syringe and warm water. If there is a live insect in the ear, cure of the pain and death of the insect are obtained by flooding the canal with pure alcohol and then removing the alcohol by means of the syringe and warm water. In using the syringe to dislodge a foreign body force should never be used. In all such cases he believes the best adage to remember is *festina lente* (never hasten quickly).

WILLIAMSON, New Orleans.

CHRONIC SINUSITIS IN CHILDREN. H. B. MARKS, New England J. Med. **216**:604 (April 8) 1937.

The patient with chronic sinusitis presents certain typical signs. Perhaps the most constant one is a purulent exudate on the posterior wall of the nasopharynx. The postnasal drip is most often seen in the morning, before the patient rises from a horizontal to a vertical position, but is also frequently seen throughout the day. This postnasal discharge, drooping from the trachea during sleep, is responsible for the various types of pulmonary lesions that are associated with chronic sinusitis. Bullen has studied 400 cases of chronic sinus disease of at least one year's duration and has found that 25 per cent of the patients have had chronic non-

tuberculous pulmonary disease in some form; 10.5 per cent had chronic bronchitis, and 8 per cent had bronchiectasis. The postnasal drip is also responsible to a certain extent for the loss of appetite, as it is continually being swallowed.

Because of the lymphatic drainage of the sinuses, it is common to find enlargement of the posterior cervical lymph nodes along the posterior border of the sternocleidomastoid muscle. The anterior nares are frequently filled with an encrusting exudate. There is a characteristic metallic odor to the breath. Frequently there are triangular areas of edema beneath the outer third of the lower eyelid over the malar prominence.

As regards treatment, at the Boston Floating Hospital the procedure has been to make an opening into the antrum, below the inferior turbinate, with a rasp. Postoperatively, irrigations of the antrums are performed daily until the returns are free from purulent material. Any treatment of chronic sinusitis which is at once complete and effective includes a program that provides for an adequate diet and avoidance of overfatigue.

GENGENBACH, Denver.

THE DEVELOPMENT AND DISORDERS OF SPEECH. T. G. WILSON, Irish J. M. Sc., March 1937, p. 135.

This is an extensive article and includes all aspects of the subject. The author describes the development of speech in an infant and child. Hearing, deaf-mutism and other problems are considered. The intelligence of the child must be considered, especially if training of a deaf child is to be carried out. The mechanical and functional disorders, such as nasal speech, stuttering and lisping, are taken up. Treatment and speech training are considered in detail. Any one particularly interested in this subject should not fail to read the article.

SNELLING, Toronto, Canada.

PREVENTION AND TREATMENT OF MIDDLE EAR INFECTIONS OF INFLUENZAL ORIGIN. M. ROSENBLATT, G. LÉVY and L. CHEYVACHMANN, Arch. de méd. d. enf. **40**:265 (May) 1937.

For more than two centuries it has been recognized that the grippal attack is a menace to the middle ear. In a review of the epidemic of grip of 1932-1933 in Moscow, it was found that 70 per cent of the children coming to autopsy because of this disease showed involvement of the structures of the middle ear; the incidence during life could not be recorded so accurately, but various authorities reported from 4.87 (Courtwiste and Cherére) to 73 per cent (Wesselle). In many cases suppurative otitis undoubtedly develops during the later stages of acute infections and can be demonstrated only post mortem. Of a series of 372 cases followed by the writers, 218 occurred in boys and 154 in girls, the ages ranging from 1 month to 8 years, which conforms with the experience of American clinicians so far as the relatively high percentage of cases in males is concerned. Among these 372 cases there were 75 invasions of the middle ear, or 20 per cent of the total. The highest percentage was found in the group from 1 to 3 years of age, the results differing in this respect from the observations of Aschoff and others, who found this complication most frequently in infants up to 6 months of age.

In the authors' series of 75 auricular involvements, 26 were unilateral and 49 bilateral, and practically all of them were associated with some other acute inflammatory disturbance of the upper airways. Precipitation tests showed a rate of from 60 to 70 mm. per hour when bronchopneumonia was present. Children who had suffered previous attacks of otitis were singularly resistant to infection during influenza, which led the authors to feel that an allergic reaction of the mucous membranes should be considered. Paracentesis was employed freely, and accurate data collected on the character of the bacterial flora. It was found that the infant on the breast reacted much more favorably than the infant artificially fed, and that associated rickets prolonged the course of the disease. Only 5 chil-

dren were subjected to exploration of the mastoid, while in a previous series of 32, 28 children were operated on. Cooperation of the otologist and the pediatrician for joint observation of these infections is urged.

AMESSE, Denver.

THE NATIONAL INSTITUTION OF PARIS FOR DEAF-MUTES. M. XÉRIDAT, Rev. méd.-sociale de l'enf. **5**:110 (March-April) 1937.

Xéridat traces the history of the institution from its rather obscure inception in the sixteenth century to its present useful state. In this school 251 deaf-mutes from 6 to 21 years of age are instructed. Only vocal, visual and tactile methods are used. The teaching of sign language was discarded in 1880.

During the first few years of instruction the children are taught regular habits, accustomed to discipline, given physical training and educated in manual labor, the identification of objects and images, reading, writing, drawing and elementary articulation. The usual school subjects (history, geography, etc.) are added to the curriculum as the child demonstrates ability and interest. Excursions to museums, factories and expositions are frequent. When the child is about 9 years of age, vocational training is instituted. The institution provides instruction in shoemaking, millinery, dress-making, carpentry, wood-carving, printing, horticulture and other trades. This full program is rounded out with adequate provision for recreation. The full fee for such instruction is 4,000 francs per year, but reductions can be obtained.

DIETRICH, Beverly Hills, Calif.

BACTEREMIAS AFTER ADENOIDECTOMY AND TONSILLECTOMY. J. F. HULK, Nederl. tijdschr. v. geneesk. **81**:2202 (May 15) 1937.

Influenced by the studies of Okell and Elliott (*Lancet* **2**:836, 1936) on bacteremia in relation to extractions of teeth, Hulk has carried out a similar investigation in 220 cases of adenotomotonsillectomy. In 24 of 100 children bacteremia was demonstrated immediately after operation (while just before tonsillectomy only 3 positive cultures were obtained, which are supposed to have been due to focal infections). In 39 of 120 other children bacteremia was also established immediately after adenotomotonsillectomy, but four hours later a positive blood culture could be obtained only from 3 of these patients. The blood cultures usually showed streptococci, which mostly belonged to the viridans or to the hemolytic group; pneumococci were found less often; staphylococci, only once. The literature, the clearing mechanism in bacteremia and the possibility of sequelae from these kinds of bacteremia are discussed.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Lungs, Pleura and Mediastinum

VARIABILITY OF THE VITAL CAPACITY OF THE LUNGS IN YOUTH. J. H. ARNETT and R. H. DE ORSAY, Am. J. M. Sc. **193**:684 (May) 1937.

In the case of 100 male and 100 female college students, the best straight line was calculated for all of the determinations of vital capacity of each student during his or her three or four years in college, and the standard deviation of the observed readings from this line was determined in each case.

A chart is given showing the deviations of vital capacity from year to year. The diagnostic value of any given vital capacity will depend chiefly on whether the loss in the given vital capacity is great in comparison with previously observed variations and whether the magnitude of the loss is commensurate with what is expected in the particular disease under consideration.

The vital capacity may be a valuable diagnostic procedure in university health services and in the hands of practitioners who have the opportunity of examining patients at intervals, especially if annual health examinations are made.

HENSKE, Omaha.

A Case Presenting Pulmonary and Osseous Lesions Presumably Due to Sarcoid. Henry F. Stoll, Ann. Int. Med. **10**:1588 (April) 1937.

A boy aged 14 years sought relief because of cough. There was involvement of the lungs and of the phalanges of the left hand. Cutaneous lesions were absent or minimal. Complete recovery took place under a regimen of restricted exercise, rest and a well balanced diet.

Reading, Galveston, Texas.

Triplicate Determinations of the Sugar Tolerance in Mild and Severe Asthma. H. C. Wagner, F. M. Rackemann and M. E. Duffy, J. Allergy **8**:353 (May) 1937.

Dextrose tolerance tests were done on twenty-four adults suffering from asthma and hay fever. Four of them had had to use epinephrine for relief at frequent intervals for several years.

The results from the capillary and venous bloods were essentially normal. The blood sugar values during fasting were in the range of those found for normal nondiabetic persons.

The blood sugar curves of the four persons who had to use epinephrine for relief fell within the range of the curves of symptom-free allergic persons. In some instances the epinephrine had to be taken within a few hours of the test, and in several instances it had to be given during the test.

The authors conclude that the blood sugar and the dextrose tolerance in allergic patients are both normal and, as a corollary, that whatever may be the fundamental nature of allergy it is not concerned with the level of the blood sugar.

Hoyer, Cincinnati.

Hepatic Necrosis. W. S. Laurie, M. J. Australia **1**:825 (May 29) 1937.

Regardless of the cause of hepatic necrosis the pathologic picture is regarded by Laurie as being similar in all cases, there being inflammation or poisoning and necrosis of liver cells followed by attempts at regeneration, with increase of fibrous tissue in the organ. The degree of these changes determines whether the liver will be large or small, smooth or nodular. Consequently, close study is urged of all cases of mild jaundice with a view to discovering possible causes. Splenectomy is urged at an early stage of the necrosis.

Gonce, Madison, Wis.

Bacteriology of Broncho-Pneumonia of Children in Egypt. M. Ali, J. Egyptian M. A. **20**:181 (May) 1937.

Cultures of material obtained by puncture of a lung were made in 101 cases of bronchopneumonia. Growth of one or more organisms was noted in 74 cases while in 27 cases no growth occurred even in cultures of material obtained by a second puncture. There were 8 pure cultures of Pneumococcus and 4 of Pneumococcus associated with other organisms; 9 pure cultures of Streptococcus and 18 of this organism associated with others; 10 pure cultures of Haemophilus influenzae and 23 of this organism associated with others; 7 pure cultures of Staphylococcus and 15 of this organism associated with others. Six other organisms were found in pure culture and associated with others.

Mulherin, Augusta, Ga.

Observations on the Etiology, Pathogenesis and Pathologic Physiology of Pneumonia in Infancy. G. Sanpaolesi, Arch. ital. di pediat. **5**:131 (April) 1937.

This is a carefully documented review of the subject, to which it adds neither new views nor new material.

Dooley, New York.

SPONTANEOUS NONTUBERCULOUS PNEUMOTHORAX IN CHILDHOOD. G. BERGHINZ, Lattante **8**:278 (May) 1937.

Short reports of two cases of spontaneous pneumothorax are given, one in a 6 month old baby with bronchopneumonia and empyema, and the other in a 13 year old girl with measles and bronchopneumonia.

HIGGINS, Boston.

INCREASED BILE PIGMENT IN THE FECES OF INFANTS WITH BRONCHOPNEUMONIA. A. GALEOTTI-FLORI, Riv. di clin. pediat. **35**:397 (May) 1937.

An increased amount of bilirubin was found in the stools of practically all of twenty-nine children with bronchopneumonia. Whereas for controls the bilirubin of the stools was between 0.046 and 0.165 Gm. per thousand grams of feces, for persons with pneumonia the figures varied between 0.185 and 0.972. Qualitative determinations indicated a parallel increase in the bile acids of the stools. No attempt was made to correlate the severity of the pneumonia with the increase in bilirubin.

HIGGINS, Boston.

RESPIRATORY MOVEMENTS SHOWN BY THE ROENTGENKYMOGRAM. E. HAGEMANN, Monatschr. f. Kinderh. **70**:174 (May) 1937.

The respiratory movements in children were studied by the roentgen kymograph. Until the twelfth or thirteenth year boys show a tendency toward thoracic breathing, while girls tend toward diaphragmatic breathing.

In infants thoracic breathing is inconsequential through the first year. Evidences of diaphragmatic breathing, which is the common type, are manifested by curves of motion as high as the second interspace. At the end of the first year thoracic respiration becomes more evident. One must conclude that in the infant the upper lobes are not of great importance in respiration.

In a case of muscle dystrophy the diaphragmatic movements were very marked.

In seven children a limitation of movement of the diaphragm on one side suggested involvement of the phrenic nerve, which might have developed from hilar or cervical adenopathy.

GERSTLEY, Chicago.

Diseases of the Gastro-Intestinal Tract, Liver and Peritoneum

ESOPHAGEAL STRICTURE DILATED WITH UROLOGIC INSTRUMENTS. H. B. FREIBERG, J. A. M. A. **108**:178 (May 22) 1937.

In cases of esophageal stricture in which the usual methods of dilatation from above are inapplicable Freiberg has found that it is practical to do a gastrostomy. A cystoscope is introduced through the wound and retrograde bougienage of the esophagus practiced. Eight patients were thus treated, with seven successful results.

BONAR, Salt Lake City.

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS. R. C. MCGAHEE, J. M. A. Georgia **26**:89 (March) 1937.

This is a statistical study of 140 cases of pyloric stenosis treated at the St. Louis Children's Hospital from 1916 to 1933.

Preoperative care and restoration of the body fluids and of the normal acid-base balance are stressed. The necessity of operation before the patient becomes athreptic is also stressed. The division as to sex and race is practically the same as found in other studies.

McGahee believes that in all cases of true hypertrophic pyloric stenosis the treatment of choice is surgical.

MORRISON, Savannah, Ga.

VOMITING IN INFANCY. W. BROWN, Edinburgh M. J. **44**:144 (March) 1937.

This communication comes from the Royal Hospital for Sick Children, Aberdeen, Scotland, and is an instalment of the author's "Clinical Recollections and Reflections." He states that the most common type of acute vomiting is associated with diarrhea due to dyspepsia, the latter being a general term for all errors and mishaps in feeding. When vomiting occurs without diarrhea the diagnosis is easier. The breast-fed baby seldom has acute vomiting due to dyspepsia. All feedings should be withdrawn for from one-half to a whole day, but fluids should be freely given. He advises administration of a solution of sodium chloride, to 3 ounces (93 cc.) of which a teaspoonful of dextrose is added. This should be given at first with a spoon, as the child may not take it voluntarily from the bottle. Saline should be administered even during continued vomiting.

Vomiting does not prove the presence of definite gastric disease, for it often is evidence of an acute condition elsewhere. Even in pneumonia it is more common than a convulsion at the onset; vomiting, however, occurs in any acute disease in which there is a sudden rise in temperature. In a case of a vomiting infant the urine and the ears should be examined.

In breast-fed babies acute vomiting is symptomatic, not dyspeptic. It may be cerebral in origin, due to meningitis, hydrocephalus, meningismus or tumor; it is produced by increased pressure on the vomiting center.

The immediate effects are rapid dehydration, loss of chlorides and collapse. Persistence may indicate overdistention, dyspepsia due to faulty feeding or obstruction to the pylorus. The result is gradual loss of weight, with "deflation" of the buttocks similar to that in celiac disease. The loose, paper-like skin indicates dehydration; the sunken fontanel, with overriding of the bones, is brought about by the reduction in spinal fluid.

The author then discusses overdistention of the stomach by food or air, dyspepsia due to faults in feeding and disturbances of the pylorus. In summary, he emphasizes the following points for observation: type of vomiting, whether of a projectile character; relation to feeding, whether immediate, in which case it is due to overdistention; character and intervals, as well as the technic, of feeding; visible peristalsis; abnormal stools; effect on the weight, and findings as a result of gastric lavage. A bulky vomitus calls for immediate relief.

NEFF, Kansas City, Mo.

HEMORRHAGIC COLITIS IN A THIRTEEN YEAR OLD BOY. L. BABONNEIX and BORGIDA, Gaz. d. hôp. **110**:288 (March 3) 1937.

The patient felt sick for eight days. The symptoms were dizziness on rising from bed, a tendency to faint once or twice a day and in the three days before entry tarry stools with streaks of red blood and of normal consistency once daily. Fever, anemia, tenderness over the spastic descending colon and a soft systolic murmur were noted. Roentgenograms indicated colitis without a visible organic lesion. The differential diagnosis is discussed. Transfusion and ice on the abdomen stopped the bleeding, the stools became normal in three days and a prompt increase in the red blood cell count was noted.

KAJDI, Baltimore.

PATHOLOGIC AEROPHAGIA IN INFANCY. H. MAGLIANO and E. HANSEN, Arch. am. de med. **13**:18, 1937.

A discussion of this syndrome based on twenty-two cases is presented. The authors differentiate between normal aerophagia, which occurs physiologically during deglutition, and excessive aerophagia (hyperaerophagia), which gives rise to pathologic manifestations. They consider nasal obstruction, even from simple coryza, feeble suckling, harelip and cleft palate, insufficient secretion of milk from the mother's breast and feeding in improper positions as the most common causes. Vomiting, colic, abdominal distention, including large tympanitic areas, and a

metallic sound produced by entrance of air in the stomach, which can be heard with the stethoscope over the epigastrium, are regarded as the most important symptoms.

In treatment the following procedure, used to induce belching, gave satisfactory results in the majority of cases: The infant is fed for from two to three minutes; he is then placed in the vertical position and, one of the attendant's hands over the abdomen and the other supporting the back, is shaken gently, as light pressure is exerted by both hands. Feeding is then continued and the procedure repeated at its termination.

SCHLUTZ, Chicago.

INTUSSUSCEPTION. B. NUMAN and J. DE REZENDE ALVES, J. de pediat., Rio de Janeiro **4**:95 (March) 1937.

Intussusception occurred in a child 7 months of age. Operation was performed thirty-five hours after diagnosis, and recovery was uneventful.

SANFORD, Chicago.

CELIAC DISEASE. A. DUARTE, J. de pediat., Rio de Janeiro **4**:184 (May) 1937.

Duarte's patient was 3 years old and recovered after banana therapy. The author reviews the etiology, symptoms and history of this disease.

SANFORD, Chicago.

HABITUAL VOMITING IN INFANCY. A. BAHIA, Pediat. e puericultura **5**:43 (March) 1937.

Many of the infants suffering from habitual vomiting have neurotic parents, but some are of good stock. Breast milk is better tolerated than other foods. Roentgenograms show that the cause is often duodenal spasm, and in these cases a sedative gives excellent results. In others it may be due to faulty eating habits, such as air swallowing. In these cases changes in feeding technic are necessary.

SANFORD, Chicago.

UMBILICAL HERNIA. O. R. DA SILVA, Rev. de gynec. e d'obst. **31**:195 (March) 1937.

A photograph shows complete eventration of the viscera in a new-born infant. Death occurred during delivery.

SANFORD, Chicago.

CONGENITAL DEFORMITIES OF THE ESOPHAGUS: A ROENTGENOLOGIC AND ENDOSCOPIC STUDY. P. G. GERLINGS, Acta pædiat. **19**:370, 1937.

The first portion of this paper is a textbook discussion of the various types of atresia of the esophagus. The advantages of esophagoscopic diagnosis are emphasized. In those rare cases in which the stenosis results from the presence of a thin diaphragm the obstruction may be relieved through the endoscope.

In the second part of the paper Gerlings discusses the less common but more remediable congenital esophageal stenosis. Usually this anomaly does not produce symptoms until the patient is several months of age, commonly when solid food is added to the diet. Two cases are reported in which the condition was treated successfully by dilatation through an esophagoscope. The first patient was 3 months old at the time of the onset of symptoms; the second patient vomited from the time of birth onward but did not come under treatment until the age of 18 months.

The third anomaly discussed is congenital short esophagus. This condition was formerly regarded as rare but is now known to be fairly common. It is frequently associated with partial ectopy of the stomach. Symptomatically either dysphagia

or pain may be present. The roentgenographic features are fairly characteristic; through the esophagoscope one may see dilatation of the upper portion of the esophagus with chronic esophagitis, stenosis of the esophagus, gastric mucosa just below the stenosis and in some cases peptic ulcer of the esophagus. The records of two cases are presented. Both patients were about a year of age; one showed an ulcer of the esophagus.

The fourth group of anomalies which is considered is that characterized by dilatation of the esophagus without any history which suggests the swallowing of caustics or the presence of spasm. This group is less well defined than the others because of the difficulty of excluding acquired stenosis and because of the lack of precise knowledge concerning the diameter of the esophagus in the healthy child. Examination of a series of normal infants showed that the esophagus becomes less distended by air when solid food is being swallowed than when liquids are being ingested.

McCune, New York.

Nervous Diseases

Phosphorus Content of the Blood Serum During the Epileptic Seizure. A. Weil and E. Liebert, Arch. Neurol. & Psychiat. **37**:584 (March) 1937.

During epileptic seizures of man the inorganic phosphorus of the serum is increased about 34 per cent. Since increase in the phosphorus of the blood in rabbits can be prevented by immobilization of the musculature by means of curare, the authors conclude that in man the increase in phosphorus must be due to the tonic-clonic contractions of the musculature during the attack.

Beverly, Chicago.

Streptococcic Otitic Meningitis with Recovery. H. Dintenfass, Arch. Otolaryng. **25**:311 (March) 1937.

The author presents the case of an 8 year old boy whose recovery is ascribed to dural incision and drainage and not to serum treatment. The results obtained lead to conjecture as to the possibilities of postural treatment, that is, raising the foot of the bed to insure adequate drainage through the incision in the dura.

Greenwood, Chicago.

A Therapeutic Possibility in Tay-Sachs Disease. S. Benjamin and A. Nachlas, Arch. Pediat. **54**:238 (April) 1937.

A case of amaurotic idiocy, or Tay-Sachs disease, occurring in a Jewish infant, a girl, is reported. Following the work of Vollmer, the authors attempted to treat the infant with a 5 per cent suspension of normal rabbit brain and medulla. The course of the disease was not arrested. The failure is attributed to the possibility that the nerve changes had progressed too far.

Orr, Buffalo.

Influenzal Meningitis: Report of a Case with Recovery. I. Cohn, Arch. Surg. **34**:398 (March) 1937.

The case of a child 11 years old in whom influenzal meningitis developed about five weeks after there had been a compound depressed fracture of the skull with laceration of the brain is reported in detail. The treatment consisted of twenty-nine spinal taps and three blood transfusions. The child made a complete recovery. No antiserum was used. The bacteriologic characteristics of the spinal fluid were well established.

Kaiser, Rochester, N. Y.

PRECOCIOUS PUBERTY FOLLOWING MEASLES ENCEPHALOMYELITIS AND EPIDEMIC ENCEPHALITIS, WITH A DISCUSSION OF THE RELATION OF INTRACRANIAL TUMORS AND INFLAMMATORY PROCESSES TO THE SYNDROME OF MACROGENITOSOMIA PRAECOX. F. R. FORD and H. GUILD, Bull. Johns Hopkins Hosp. **60**:192 (March) 1937.

Two cases of precocious sexual development in young girls following measles encephalitis are described, and another case of premature development of the sex organs and of sexual misbehavior in a boy following epidemic encephalitis is discussed.

A survey of the literature seems to indicate that destructive lesions in the region of the pineal body and in the walls of the third ventricle may result directly or indirectly in the syndrome of macrogenitosomia praecox. Cases are cited in which this syndrome was associated not only with tumors arising in the region of the pineal body but with tumors of the hypothalamus. The same syndrome is known to follow inflammatory processes, such as meningitis, meningo-encephalitis and epidemic encephalitis.

The information available at present indicates that the pineal body plays no significant rôle in the production of macrogenitosomia praecox, for this gland is normal in many cases in which this syndrome is fully developed and destruction of the pineal body may be followed by no apparent change in the genital organs. We have failed to find a single instance in which definite macrogenitosomia praecox has been associated with a verified pinealoma.

FROM THE AUTHORS' SUMMARY.

THE USE OF PARA-AMINO-BENZENE-SULPHONAMIDE OF ITS DERIVATIVES IN THE TREATMENT OF BETA HEMOLYTIC STREPTOCOCCAL MENINGITIS. FRANCIS F. SCHWENTKER, FREEMAN P. CLASON, WILLIAM A. MORGAN, JANVIER W. LINDSAY and PERRIN H. LONG, Bull. Johns Hopkins Hosp. **60**:297 (April) 1937.

The case histories of four patients ill with meningitis due to the beta hemolytic streptococcus have been described. Three of these four patients recovered. All were treated with sulfanilamide (para-amino-benzene-sulfonamide) or its derivatives.

The authors believe that surgical procedures to eradicate septic foci are indicated in streptococcic meningitis as an adjunct to specific therapy but that extensive surgical intervention should not be resorted to until the infection has been brought under control by the specific therapy.

LYTTLE, New York.

EPILEPSY IN CHILDHOOD: I. A STATISTICAL STUDY OF CLINICAL TYPES. L. WILKINS, J. Pediat. **10**:317 (March) 1937.

This paper is a statistical study of the types of epilepsy seen over a period of seven years in a special clinic for epileptic children at the Harriet Lane Home of the Johns Hopkins Hospital. From this study were excluded children suffering from hysterical episodes, temper tantrums, breath-holding attacks, spells of syncope, febrile convulsions, tetany, acute neurologic lesions, syphilis of the central nervous system or recognizable tumor of the brain. After patients with these conditions and the children who had not been observed for a sufficiently long period had been excluded, the studies were based on 254 non-institutionalized children who were thought to have epilepsy. Encephalography was not done as a routine.

Classification of the patients as those with "organic" and those with "essential" epilepsy was not possible, but Wilkins believes that many epileptic persons with severe mental defects may have organic cerebral lesions, which frequently are impossible to determine; he divided the patients, therefore, into the following groups: (1) patients with an intelligence quotient above 80 and no evidence of neurologic lesions (43.7 per cent); (2) patients with an intelligence quotient below 80 and no other evidence of neurologic lesions (32.3 per cent), and (3) patients

with definite evidence of neurologic lesions (24 per cent). The diagnosis of neurologic lesions was made on the basis of the following symptoms: hemiplegias and monoplegias; constant localization of convulsions, with or without neurologic signs, and a history indicative of lesions of the brain, with absence of signs such as birth injury, fracture of the skull, transient paralyses, lead encephalitis or probable epidemic encephalitis. Fifty-four per cent of all the patients studied had intelligence quotients above 80. In 57.5 per cent of the patients without neurologic lesions as compared with 41.5 per cent of those with such lesions, the intelligence quotients were above 80.

The character of the seizures was studied in the three groups. The author distinguishes between minor motor and petit mal attacks. The latter are characterized by momentary lapses of consciousness without motor manifestations. Sixteen, or 6.3 per cent, of the patients had attacks exclusive of the petit mal type. Fifteen of these were children of normal mentality. The petit mal attack was the predominant feature in 20.7 per cent of the group with normal mentality and in 6.1 per cent of the group of retarded children. The typical petit mal attack was not encountered in any of the patients with conditions diagnosed as neurologic lesions. The motor attacks and the convulsive discharge were the predominant features in 96.7 per cent of the children with neurologic lesions, in 69.5 per cent of those with mental retardation and in 62.2 per cent of those with approximately normal mentality.

A study of the frequency of seizures in the three groups did not give a correct indication of the severity of the disease, owing to the fact that petit mal seizures are more common among children of normal mentality. Convulsive attacks were less severe and less frequent among the group of children with normal mentality, and, conversely, the severe forms occurred more frequently in the group suffering from mental defects. The symptoms of epilepsy are most liable to appear in the first two years of life. There are a decrease in the number of cases in which the disease commences between the second and the sixth year and another increase in the frequency of onset between the sixth and the eighth year. Other workers have shown a third period of increase from the tenth to the fifteenth year, but this is not indicated in the author's studies because of the small number of children in this age group in his series. The early onset, before the second year, is especially common in children having neurologic lesions, since many of these lesions are the result of birth traumas and congenital malformations.

RAUH, Cincinnati.

EPILEPSY IN CHILDHOOD: II. THE INCIDENCE OF REMISSIONS. L. WILKINS, J. Pediat. **10**:329 (March) 1937.

This is a statistical study of the incidence of remissions in noninstitutionalized epileptic children observed in the clinic for epileptic children at the Harriet Lane Home. Children receiving ketogenic diets or under intensive dehydration regimens were not included in this study. Of 200 epileptic children, remissions of one year or longer were encountered in 46, or 23 per cent, and remissions of two years or longer, in 19 per cent. These figures correspond closely with those of other workers. In the author's opinion, the principal factors which influence the prognosis for remissions are the number and frequency of the attacks. The incidence of remissions was 41 per cent in patients whose attacks occurred less frequently than once a month, as compared with 16 per cent in patients having attacks monthly or oftener. Remissions occurred in approximately 30 per cent of the children with nearly normal intelligence and without neurologic lesions, whereas they were encountered in only 20 per cent of the children with mental defects or neurologic lesions. Remissions occurred twice as frequently in patients (from 23 to 25 per cent) having generalized or localized convulsions or minor motor seizures as in those (12.5 per cent) whose attacks were predominantly of the petit mal type (12.5). Thirty of the 46 remissions were in patients whose disease was of less than five years' duration. The age of the patient at the onset of epilepsy seemed to have no influence on the liability to remissions.

Nine of the children were receiving no medication at the time of cessation of seizures. Of these 9 children, 5 were suffering from mild attacks, and 4 had very severe forms of epilepsy with innumerable attacks occurring over many years. Of the 37 patients receiving medication at the time of remission, 14 had mild forms of epilepsy, the remaining 23 suffering from the severe form, of long duration. In some cases the sedative drugs administered caused immediate cessation of attacks or gradual improvement, followed finally by freedom from seizures. In other cases sedative therapy seemed to cause no improvement for a long time, and then, without any change in treatment or obvious cause, sudden improvement and cessation of attacks occurred. Wilkins does not imply that sedatives are not of value in the treatment of epilepsy, but he states that spontaneous remissions may occur in the most severe forms and that it is exceedingly difficult to evaluate any therapeutic cure.

Wilkins feels unable to discuss the prognosis for permanent cure. Long periods of remissions are not uncommon, especially during the period of adolescence. He quotes from Turner: "It is unsafe to regard as cured any case of epilepsy in which the seizures have been in abeyance for a period of less than nine years."

RAUH, Cincinnati.

EPILEPSY IN CHILDHOOD: III. RESULTS WITH THE KETOGENIC DIET. L. WILKINS, J. Pediat. **10**:341 (March) 1937.

This report is based on 30 noninstitutionalized epileptic children treated with the ketogenic diet. These children presented no evidence of organic cerebral lesion, and all but 3 had an intelligence quotient above 80. In nearly all instances the children were suffering from severe epilepsy and were subject to frequent attacks; a considerable proportion of the patients were subject to petit mal attacks. The diet given was one with a ratio of fats to carbohydrates and proteins of 4:1. In many cases a period of starvation of from three to seven days preceded the diet. In a number of cases other forms of therapy, such as sedatives, production of acidosis by means of ammonium chloride and administration of diets low in salt and of theobromine with sodium salicylate, were included, and psychologic and environmental adjustments were attempted. Eight patients became free from attacks for from one and a half to six years. Four patients had freedom from attacks for periods lasting from nine to fifteen months. In these cases the diet was discontinued when relapses occurred. Drugs were not given in these cases, and in only 1 instance was the patient's cooperation in the dietary regimen perfect. In the remaining 3 cases relapse was associated with increasing laxity in the diet and failure to maintain ketosis.

In 3 patients the course of the disease seemed to be influenced favorably for a short period after institution of the diet. These patients did not have remissions, and subsequently the disease became as severe as before. Fifteen patients (50 per cent) showed no response to treatment.

Wilkins believes that on the whole the treatment may be considered to have had some degree of success, for almost all the patients treated with a ketogenic diet had severe forms of epilepsy and the expectancy of remission in these patients was considerably less than the average. Seven of the patients who had remissions had had epilepsy for less than three years, which may be of significance in the prognosis for success. In some cases it was impossible to decide whether the ketogenic diet was directly responsible for the remission or amelioration of the disease. In other cases the use of sedatives with the diet obscured the interpretation. Wilkins feels unable to evaluate scientifically the results obtained with the ketogenic diet but thinks that its trial in the treatment of epilepsy is justified whenever attacks remain uncontrolled by sedatives.

RAUH, Cincinnati.

OTITIC BRAIN ABSCESS. N. O. EADDY and R. SEKERAK, J. South Carolina M. A. **33**:49 (March) 1937.

An excellent review of abscess of the brain is given by the authors, with a report of fourteen cases. The signs varied according to the location of the abscess.

Intermittent headache was persistently present, associated with vomiting in all but one case. The pulse rate showed considerable fluctuation, while the oral temperature in this series of cases did not exceed 101 F. except in terminal stages. A history of chronic otitis media is usually present. The treatment is surgical, by incision and drainage.

WESTON JR., Columbia, S. C.

THE TRYPTOPHANE REACTION IN THE CEREBRO-SPINAL FLUID. J. SPILLANE, Lancet **1**:560 (March 6) 1937.

The successful demonstration of the tubercle bacillus often demands an inordinate expenditure of time, and so attention has been directed to other methods of examining the fluid with the object of discovering some specific reaction. The demonstration of tryptophan bodies seems the most promising. It is suggested that tryptophan is synthesized by tubercle bacilli in the fluid.

The test is inapplicable in purulent, hemorrhagic or xanthochromic fluids, a "false positive" reaction being given in such cases.

The test is as follows: To 3 cc. of cerebrospinal fluid in a test tube are added 15 cc. of concentrated hydrochloric acid and 2 or 3 drops of a 2 per cent dilution of solution of formaldehyde U. S. P. (freshly prepared). The mixture is shaken and allowed to stand. It is then gently floated on 2 cc. of a 0.06 per cent solution of sodium nitrate (freshly prepared).

A positive reaction consists of the formation of a delicate violet ring (in two or three minutes).

LANGMANN, New York.

INFLUENZAL MENINGITIS WITH COMPLETE RECOVERY. K. H. TALLERMAN, Proc. Roy. Soc. Med. **30**:707 (April) 1937.

The case reported was that of a child 2½ years old. He was admitted to the hospital July 9 with a history of having caught cold five days previously and of having a shaking fit three days afterward in which he fell forward and subsequently lapsed into sleep.

Lumbar puncture was performed, and a faintly turbid fluid was obtained, under pressure. No organisms were found. Next day a culture of the cerebrospinal fluid gave a scanty growth of Pfeiffer's bacillus. Specimens of cerebrospinal fluid obtained on July 16 and 30 again showed on culture a growth of Pfeiffer's bacillus. After July 30 all cultures taken were sterile.

The boy was discharged from the hospital on September 12, apparently normal in every respect, physically and mentally.

WILLIAMSON, New Orleans.

INFLUENZAL MENINGITIS WITH COMPLETE RECOVERY. T. P. WILLIAMS, Proc. Roy. Soc. Med. **30**:877 (Feb.) 1937.

An infant of 9 months fell and struck her head, after which she remained drowsy. Two days later she vomited, became blue and refused food. The same day she was admitted to the hospital in a condition of collapse. There was no paresis or rigidity. Her temperature was 102 F. Four days later she had a series of convulsions, and her temperature rose to 104 F. The neck became rigid, and the fontanel commenced to bulge. Lumbar puncture was performed, and the fluid was found under pressure. It gave a free growth of influenza bacilli. Daily punctures were carried out with free drainage, and the child made an uneventful recovery.

WILLIAMSON, New Orleans.

COCHLEOVESTIBULAR REACTIONS IN FRIEDREICH'S ATAXIA AND SIMILAR HEREDODEGENERATIVE DISEASES. G. GUILLAIN, P. MOLLARET and M. AUBRY, Rev. neurol. **63**:36 (Jan.) 1935.

Since no study of vestibular and cochlear function in patients with Friedreich's ataxia has been recorded, the authors performed tests on sixteen patients of this type. In addition, they studied five patients with hereditary cerebellar ataxia, and

one with familial spasmodic paraplegia (Roussy-Lévy disease). These tests have been repeated annually for six years. The authors conclude that although the auditory function is almost always normal, Friedreich's disease produces progressive hypo-excitability of the vestibular apparatus, as shown by caloric and rotation tests. They affirm that this difference provides a differential point in the diagnosis of familial ataxia.

DAFFINEE, Boston.

HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE) COMPLICATED BY BLOOD CHANGES. E. GJONYS and G. E. SCHRODER, Rev. neurol. **63**:79 (Jan.) 1935.

A case is presented in a boy of 12 years. The onset was atypical and vague. Myelocytes (from 2.5 to 11 per cent) were constantly present. The spleen was enlarged. Careful studies were made over a period of two years. The observations at autopsy are given in detail.

DAFFINEE, Boston.

LEFT HEMIPLEGIA IN AN INFANT OF TWENTY-TWO MONTHS: MICROGYRUS WITH CORTICAL HETEROTOPIES. L. BABONNEIX and J. LHERMITTE, Rev. Neurol. **63**: 403 (March) 1935.

This boy was admitted at the age of 22 months, with hemiplegia, which dated from convulsions at the age of 5 months. He contracted bronchopneumonia at 26 months, and a month later typical measles, with pneumonia, to which he succumbed. Autopsy showed a microgyrus on the right, with abnormal outgrowths of gray matter. There were numerous isolated islets of gray matter scattered through the centrum ovale.

The authors believe the cortical alterations were due to changes in the cerebral vascular system, on an infectious basis, which occurred at a very early age—perhaps in utero.

DAFFINEE, Boston.

PURULENT MENINGITIS CAUSED BY PROTEUS VULGARIS. E. PELUFFO, C. LEDESMA and R. C. GEAGUSTINI, Arch. de pediat. d. Uruguay **8**:108 (Feb.) 1937.

The authors present suppurative meningitis caused by Proteus vulgaris in a 28 day old infant. A cerebrospinal block complicated the condition and limited the accumulation of purulent material to the ventricular system In spite of repeated punctures it was practically impossible to check the increase of pressure in the ventricles. The therapy consisted in irrigation of the ventricular system with physiologic solution of sodium chloride containing small amounts of methenamine ethylhydrocupreine sulfate, acriflavine hydrochloride and autogenous vaccines. None of these drugs produced any beneficial results, and two months after the onset the infant died in an athreptic condition with diphtheric rhinitis and bronchopneumonia.

SCHLUTZ, Chicago.

HYDROMYELIA IN INFANCY. J. WOLF, Monatschr. f. Kinderh. **69**:371 (March) 1937.

The case of a 9 month old infant in whom perspiration occurred only on the left side is reported. On the right side reflexes as well as reaction to heat, cold and pain, were absent. In view of the increased pressure of the spinal fluid, Wolf believes the case to be one of hydromyelia.

GERSTLEY, Chicago.

Psychology and Psychiatry

SOME CHANGES IN DELINQUENTS DURING INSTITUTIONAL COMMITMENT. NEWELL C. KEPHART, J. Juvenile Research **21**:67 (April) 1937.

This article raises one of the most important questions that confronts those who are interested in the efforts made by the state to care for all who do not fit

into the social structure. It is the question of the effect of institutionalization on human beings. It would appear from this article, emanating as it does from an institution of the highest character, that any institutionalization can be unfortunate. The reasons for the failure of commitment are obviously varied. One, however, is suggested by the fact, not noted in this article, that children who are placed in institutions feel that their commitment is of the nature of punishment. There are two types of reaction to this feeling, the psychoneurotic (fear) and the delinquent (bravado). To the reader who is not familiar with the mathematics of statistics the conclusions are somewhat beclouded, but one gets the impression that the results indicate an increase rather than a diminution in the subject's difficulties.

HAMILL, Chicago.

CONFESSION TESTS. HOMER KENTON MOORE, J. Juvenile Research **21**:76 (April) 1937.

"Confession Tests" is a somewhat ambiguous heading. The results seem to have impressed Moore with the lack of frankness obtained in these tests. As is true in all work with children, two phases of the sense of insecurity, fear and bravado, are seen in the results of the questions asked. A list of forty questions to be answered "yes" or "no" make up the "personal data blank." These questions and the answers to them make up the sum total of the so-called confession.

HAMILL, Chicago.

PSYCHE AND CHOREA MINOR. F. GRANONE, Arch. ital. di pediat. **5**:173 (April) 1937.

Granone has made a psychologic study of eight children with chorea, and recorded his findings in the form of a psychogram. He presents only preliminary results, which do not admit conclusions but indicate the value of the method. Incidentally, three of the children were of superior intelligence, one of average, and five of inferior intelligence.

DOOLEY, New York.

MONGOLISM AND ITS TREATMENT. P. LEREBOULLET, Lattante **8**:248 (May) 1937.

The following established facts regarding mongolism can serve as a basis of treatment: (1) retarded growth, (2) endocrine alterations, (3) excessive nervousness, (4) frequency of congenital syphilis and (5) adaptability to specialized education. The treatment used by Lereboullet consists of a definite regimen for the child, medication with phosphorus, calcium, iodine and vitamins, giving thyroid and thymus and occasionally of adrenal and hypophysial gland products, daily use of phenobarbital and antisyphilitic measures. Educational policies aim at avoidance of too great excitement, cultivation of talents, such as that for music, assurance of affection for those who work and live with them and development of the capacity to concentrate and to speak clearly and well. While such treatment leaves the mongolian still far from being a normal child, it has been found sufficiently encouraging to justify further efforts.

HIGGINS, Boston.

PSYCHOTHERAPY AND PEDAGOGY. LEOPOLDO MATA, Bol. Inst. internac. am. de protec. a la infancia **10**:519 (April) 1937.

The concept of the new pedagogy should be directed into new channels, so that it can be adapted to the new postulates of science. Among these postulates, psychobiology occupies a prominent place.

The large contribution of modern experimental psychology to pedagogic practice and that of related branches which have helped to clarify numerous problems for the better knowledge of man and of his behavior problems make it necessary to modify systems and points of view related to the teaching of children.

This fundamental revision should include, as an essential part of its scope, an improved scientific criterion for the development of teachers.

Old educational methods, still prevailing in part, should be provided with the flexibility and adaptation necessary to finish rooting out dogmatism and prejudice and to enable them to face the orientation of the human personality on the basis of a wide view of biologic facts.

The specialist in neuropsychiatry of children, the school psychologist and the teacher, developed on broader programs for psychobiology in the school, should be the elements forming the new school, which is to be directed toward a wider and improved pedagogy founded on experimentally demonstrated scientific truths.

FROM THE EDITOR'S SUMMARY.

MONGOLOID IDIOTS ATTAINING A GREAT AGE. C. SIMONS and N. SPEYER, Nederl. tijdschr. v. geneesk. **81**:2344 (May 22) 1937.

In three cases of mongoloid idiocy, which the authors describe, the patients were, respectively, 40, 63 and 83 years old. The attainment of such an age as the last cited is absolutely a rarity. VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Genito-Urinary Tract

THE TREATMENT OF UNDESCENDED TESTES WITH ANTERIOR PITUITARY-LIKE SUBSTANCE. W. O. THOMPSON, A. D. BEVAN, N. J. HECKEL, E. R. MCCARTHY and P. K. THOMPSON, Endocrinology **21**:220 (March) 1937.

The effects of treatment with the anterior pituitary-like substance from the urine of pregnant women on twenty-one undescended testes in eighteen boys from 1½ to 17 years of age are reported. The dose was commonly 200 rat units three times a week for an average of five months. Descent occurred in four patients (19 per cent), in all four of whom the testis was in the inguinal canal before treatment.

In seven other patients treated surgically after prolonged administration of anterior pituitary-like substance, anatomic factors making descent impossible were present.

The authors conclude that operative procedures appear to be necessary in most cases of undescended testes but should be preceded by from four to six months of treatment with anterior pituitary-like substance.

One of the authors (A. D. B.) in a separate note states his opinion that the glowing reports in the literature are exaggerations and questions the value of bringing on changes which simulate artificial puberty in a child of 7 or 8 years. But since he has observed no evidence of injury he concurs in advising treatment with anterior pituitary-like substance. JACOBSEN, Buffalo.

EVALUATION OF HORMONE THERAPY FOR UNDESCENDED TESTES IN MAN. A. J. CRAMER JR., Endocrinology **21**:230 (March) 1937.

After reviewing the physiologic aspects of testicular descent, the pathologic nature of undescended testes and the experimental work on animals, Cramer discusses the clinical results of treatment of undescended testes with extracts of the urine of pregnant women. A tabulation of all the cases in man in which this treatment was used reported to date, including twenty recorded in this paper, making a total of eighty-one, indicates complete descent after treatment in 71.6 per cent, a partial result in 16 per cent and failure in 12.4 per cent.

A dose of 100 rat units of the anterior pituitary-like gonadotropic substance from the urine of pregnant women given twice a week until a total dose of from 500 to 5,000 rat units was reached produced complete descent in thirteen cases, partial descent in four and failure in three.

The conclusion is that the evidence is sufficient to consider hormone treatment a valuable method of therapy for undescended testes. When surgical correction is indicated the results may be enhanced by the use of hormone therapy as an adjunct.

JACOBSEN, Buffalo.

THE BACTERICIDAL POWER OF THE URINE AFTER THE ADMINISTRATION OF PRONTYLIN (SULFANILAMIDE) BY MOUTH. H. F. HELMHOLZ, Proc. Staff Meet., Mayo Clin. **12**:244 (April 21) 1937.

The urine of patients taking sulfanilamide acquires definite bactericidal power for the organisms commonly found in the urinary tract.

MILLER, South Bend, Ind.

AN UNUSUAL CASE OF HERMAPHRODITISM. HAROLD CHAPPLE, Brit. M. J. **1**:802 (April 17) 1937.

The report concerns an interesting and unusual case. In brief, it is that of an otherwise normal, possibly oversexed, young woman, without a uterus and with an undescended testis. However, she showed preference for men rather than for women—in other words, there was no homosexual depravity. Factors that determine sex are discussed from the point of view of a general sex problem. No special conclusion is drawn.

ROYSTER, University, Va.

FREE CHOLESTEROL IN THE PATHOGENESIS OF DIABETES INSIPIDUS OF CHILDREN. S. STEFANINI, Med. inf. **8**:69 (March) 1937.

Seven cases of diabetes insipidus were studied, and determinations of the free cholesterol content and the value for cholesterol esters of the blood serum were made.

The data obtained are summarized in the following table:

Cholesterol Content in Grams per Thousand Cubic Centimeters

	Total	As Ester	Free
Normal	1.60-1.80	1.00-1.20 (60%)	0.60-0.80 (40%)
In diabetes insipidus	1.54-2.40	0.59-0.83 (33-38%)	0.95-1.57 (62-67%)
Average	2.07	0.71 (35%)	1.30 (65%)

In one patient, the giving of solution of posterior pituitary reduced the total cholesterol content from 2 to 1.84 Gm. and the amount of free cholesterol from 1.35 to 0.89 Gm., and raised the value for cholesterol esters from 0.65 to 0.95 Gm.; the percentage of cholesterol as esters rose from 33 to 52.

In the syndrome of Hand, Schüller and Christian (exophthalmos, bony alterations and diabetes insipidus) these are changes similar to those just recorded. Diabetes insipidus is believed to belong to the same clinical unit as Hand-Schüller-Christian's syndrome and to represent an intermediate state in this xanthomatous dyscrasia.

HIGGINS, Boston.

THE TREATMENT OF BED WETTING. T. SUTTER, München. med. Wchnschr. **84**:585 (April 9) 1937.

Bed wetting occurs only when the patient is lying on his back. To prevent the patient from assuming this position Sutter ties a towel around the patient's waist, so that the knot is in the back. The discomfort of resting on the knot will cause the patient to sleep on his side or abdomen. Although this procedure works well, other forms of treatment should not be disregarded.

BRAHDY, Mount Vernon, N. Y.

RELATIONSHIP BETWEEN SPINA BIFIDA OCCULTA AND THE URINARY TRACT. H. HIPPE and K. HÄHLE, Röntgenpraxis **9**:195 (March) 1937.

Among 1,146 cases in which roentgen examination of the skeleton was made, spina bifida was found in 412 (36 per cent); some roentgen abnormality of the urinary tract was demonstrated in 160 of these cases (39 per cent). Among the 1,146 cases, the lumbar and sacral portions of the spine were found to be normal in 734; in the normal group only 103 patients (14 per cent) were shown to have roentgenographic anomalies of the urinary apparatus. Hippe and Hähle do not mention the criteria which they employed to evaluate the anatomic status of the urinary tract. They accept the statistics just given as providing proof of the existence of a positive correlation between the presence of spina bifida occulta and anatomic anomalies of the kidneys, ureters and bladder.

McCUNE, New York.

Diseases of the Ductless Glands; Endocrinology

EXTIRPATION OF A HUGE PINEALOMA FROM A PATIENT WITH PUBERTAS PRAECOX: A NEW OPERATIVE APPROACH. G. HORRAX, Arch. Neurol. & Psychiat. **37**:385 (Feb.) 1937.

Horrax reports the extirpation of a pinealoma weighing 70 Gm. from a child showing the clinical picture of pubertas praecox. He describes a more radical means of exposing the pineal region and suggests that it should be the procedure of choice.

BEVERLY, Chicago.

A CASE OF SUPPOSED PROGERIA IN A GIRL AGED SEVENTEEN MONTHS. A. STERN and D. P. LIEBERMAN, Arch. Pediat. **54**:169 (March) 1937.

Stern and Lieberman present the case of an infant prodigy, a girl 17 months old who can walk, talk, sing and dance, though she weighs but 11 pounds (5 Kg.). The diagnosis of progeria is entertained because of the suggestive facial appearance and the unusual mental development and motor control. The changes in the osseous system are not definite.

ORR, Buffalo.

THE EFFECTS OF THYROIDECTOMY, CASTRATION, ANTERIOR LOBE ADMINISTRATION AND PREGNANCY UPON EXPERIMENTAL DIABETES INSIPIDUS IN THE CAT. W. R. INGRAM and C. FISHER, Endocrinology **21**:273 (March) 1937.

In a series of previous papers by Ingram and Fisher dealing with the experimental production of polyuria in cats and monkeys evidence has been presented to show that permanent polyuria as produced in such forms is associated with lesions interrupting the nervous pathway extending from the nucleus supra-opticus to the posterior lobe of the hypophysis. These animals are unusually sensitive to the diuretic effects of feeding thyroid and salt.

In this paper the observation previously made, that thyroidectomy may somewhat reduce but does not abolish the polyuria produced by lesions of the supra-opticohypophysial system in cats, has been confirmed in four other cats. Feeding desiccated thyroid to such animals elevated the water exchange to a level equal to or exceeding that existing before thyroidectomy. Castration performed on four cats with diabetes insipidus failed to diminish the polyuria, and in one of these the water exchange increased after ovariectomy.

Administration of a crude anterior lobe preparation, while ineffective in producing polyuria in normal cats, may increase the water exchange in cats with a tendency to diabetes insipidus. It is not invariably effective, however, and cats already displaying marked polyuria may not respond to such treatment.

JACOBSEN, Buffalo.

SOME EFFECTS OF SYNTHETICALLY PREPARED MALE HORMONE (ANDROSTERONE) IN THE RAT. C. R. MOORE and D. PRICE, Endocrinology **21**:313 (May) 1937.

In this study the authors determined the effects of androgen crystalline androsterone when in oil solution it had been injected subcutaneously into castrate and normal male rats. In castrate rats it maintained the secretory function and normal rate of growth of the prostate gland and seminal vesicles or, given later, repaired castration damages. When injected into young normal males it reduced testicular weights to from 12 to 50 per cent of those of the litter mates used as controls; in mature rats, however, large doses were not injurious to the testicles. In the pituitary glands of the androsterone-treated normal males gonadal stimulating properties were lower than in the pituitary glands of untreated normal controls, a fact which suggests that the testicular damage done by androsterone is indirect, by virtue of its action on the intact pituitary.

Species differences must be emphasized since in another rodent, the annual breeding ground squirrel, androsterone gave pronounced testicular responses, i. e., increase in size and earlier appearance of spermatozoa.

As in the case of extracts of the testes of bulls, this study failed to reveal stimulation of the testicle by androgen either in gross size, spermatogenic activity or hormonal secretion. On the contrary, both caused decided injury to the normal testicle in the early stages of growth.

JACOBSEN, Buffalo.

EFFECT OF FEMALE SEX HORMONES UPON THE OXYGEN CONSUMPTION RATE OF NORMAL RATS, AND UPON THE TOLERANCE TO DESICCATED THYROID. D. N. DANFORTH, R. R. GREENE and A. C. IVY, Endocrinology **21**:361 (May) 1937.

It has been found that the thyroid gland is specifically inhibited by estrogen. In this paper Danforth, Greene and Ivy report that the rate of the consumption of oxygen does not change significantly after the administration of estrogen and that it increases more in animals which receive desiccated thyroid alone than in those which receive estrogen plus a similar amount of thyroid. But there is a physiologic limit beyond which the metabolic effect of orally administered thyroid cannot be inhibited by estrogen in excess.

JACOBSEN, Buffalo.

BLOOD CHEMISTRY OF SURVIVING PARATHYROIDECTOMIZED DOGS. E. I. EVANS, S. SZUREK and R. KERN, Endocrinology **21**:374 (May) 1937.

Although considerable attention has been directed to the treatment of the tetany which occurs in dogs a few days after complete extirpation of their parathyroid glands, little work has been done on the factors responsible for the subsidence and gradual disappearance of this symptom complex. The authors therefore studied the inorganic constituents of the blood of animals that had completely recovered from this complex. Their conclusions were as follows: Low serum calcium and high serum inorganic phosphorus, which according to some workers should precipitate tetany in the parathyroidectomized dog, do not in parathyroidectomized dogs during their period of survival. In the parathyroidectomized dog serum calcium and inorganic phosphorus can remain at tetany levels for at least nine months without returning to normal. After parathyroidectomy there are no significant changes in sodium, potassium, magnesium and the chlorides during the period of survival.

The presence of accessory parathyroid tissue does not explain the survival of all parathyroidectomized dogs, since such dogs may survive for at least nine months with low serum calcium and high inorganic phosphorus. The authors are of the opinion that a neuromuscular adjustment in the animal allows bodily functions to go on apparently normally, with absence of tetany even though abnormal calcium-phosphorus and calcium-sodium-potassium ratios are present.

JACOBSEN, Buffalo.

CARBOHYDRATE METABOLISM STUDIES IN HYPOPHYSECTOMIZED RATS. L. T. SAMUELS and H. A. BALL, Endocrinology **21**:380 (May) 1937.

Rats which had been hypophysectomized two and a half weeks or less before the test and had fasted for twenty-four hours were given 1 Gm. of dextrose per hundred grams of body weight by stomach tube. They yielded curves similar to those found for normal animals with the same dose. However, when this amount of dextrose was given by stomach tube five weeks after operation, a high curve of diabetic type resulted. In contradistinction to alimentary administration, if the aforementioned dose or half the amount was given subcutaneously, abnormally high sugar curves resulted as soon as one week after hypophysectomy. The inability to remove excess sugar from the blood increased progressively in severity for a period of several weeks. This suggests an indirect effect of removal of the pituitary gland.

A decrease of 36 per cent in the rate of intestinal absorption of dextrose explains why the blood sugar curves in the animals which received the sugar in this way did not show higher than normal curves during the first two and a half weeks following hypophysectomy. This deficiency in intestinal absorption of dextrose appears abruptly after removal of the pituitary gland and once it is established it remains constant. This suggests a direct effect of pituitary deprivation.

JACOBSEN, Buffalo.

A STUDY OF THE METABOLISM OF A DWARF UNDER TREATMENT WITH GROWTH HORMONE. H. C. STRUCK and S. A. SZUREK, Endocrinology **21**:387 (May) 1937.

A female dwarf aged 24 years was treated with an extract of the anterior lobe of the pituitary gland containing the growth hormone over a period of three and a half months. A study was made of the nitrogen, calcium and phosphorus balances before, during and after the treatment. Nitrogen was retained, but the calcium and phosphorus balances remained essentially unchanged. An increase in weight of 11½ pounds (5.2 Kg.) was the only change noted in the patient's condition.

She had had influenza with coma at the age of 9 years, following which she failed to grow. Menses never occurred, and later marked difficulties of behavior developed. The intelligence quotient was less than 30. She died unexpectedly following appendectomy. The impression of the pathologist was that there had been "general involvement of the endocrines" although, contrary to expectation, the hypophysis was macroscopically and microscopically the most nearly normal of the endocrine glands except the adrenals.

JACOBSEN, Buffalo.

PUBERTAS PRAECOX (MACROGENITOSOMIA). H. P. RUSH, J. B. BILDERBACK, D. SLOCUM and A. ROGERS, Endocrinology **21**:404 (May) 1937.

The most significant symptoms of hypergenitalism are premature and excessive development of the genitals, premature change in the voice and rapid excessive development of the body in general. The skeleton is influenced in an interesting manner; at first and for several years the boy is large for his age, as if he were becoming a giant, but the excessive output of testicular incretions hastens epiphysial unification, and premature closure of the latter transposes a misleading and transitory gigantism into a final height which is not excessive and which may indeed incline toward mild dwarfism. Roentgenograms of such boys reveal a bone age in advance of their chronological age as additional proof of precocity.

The cases may be divided into three groups: (*a*) a group in which the condition is a primary constitutional one, with no incretory or physical abnormality discoverable; (*b*) the endocrine group, in which there have been found tumors of the ovary and of the pineal and adrenal glands and in which there is the theoretical possibility of excess gonadotropic hormone of the anterior lobe of the pituitary gland, also a possibility that the thymus gland may be responsible in some cases; (*c*) the cerebral group, in which the condition develops after encephalitis or in association with hydrocephalus or tumor of the brain.

Here is reported an unusual family in which all male members, the father and both sons, developed precociously. The rapid development began at the ages of 5, 1½ and 3 years, respectively. The paternal grandfather and the great grandfather also showed this development. There were also two great uncles and one distant cousin (male) who had the same history—eight known instances in four generations. Androgen was demonstrated in the urine of the father and two sons by the capon comb test. Normally it is not found in boys under 10 years of age. Gonadotropic substance could not be demonstrated by the action of an extract of the urine on immature female rats in any of the cases. No associated signs or symptoms were present to suggest tumor or marked hypertrophy of the pineal gland, adrenal cortex, gonads pituitary gland or thymus. There were no signs or symptoms of a cerebral lesion. These cases seem to fall into the group of primary, primary-constitutional or congenital pubertas praecox.

One must bear in mind that the possibility of a hereditary factor causing the germinal cells to be stimulated by less than a normal amount of "hormone" may be the explanation in the constitutional group.

JACOBSEN, Buffalo.

PROTAMINE INSULIN IN JUVENILE DIABETES. H. R. DRYSDALE, J. A. M. A. **108**: 1250 (April 10) 1937.

Ten diabetic children were carefully selected for this study with respect to intelligence and cooperativeness, uncomplicated diabetes and the necessity of insulin for diabetic control. The results with protamine insulin have been encouraging, and it has been found that hospitalization during the shift from regular insulin is not entirely essential. In these patients all the insulin is being given before breakfast. Hypoglycemic reactions with protamine insulin are comparatively rare but may be insidious in onset and severe. No local subcutaneous reactions have been noticed. The preparation seems to prevent diabetic acidosis in infections, although glycosuria may be profuse. Some evidence points to the fact that protamine insulin may raise the renal threshold in some instances. The preparation is valuable when administered to "insulin wasters."

BONAR, Salt Lake City.

LATE RESULTS OF TREATED CHILDHOOD HYPOTHYROIDISM: TWO CASE REPORTS. L. M. BAYER and A. W. SNOKE, J. Pediat. **10**:361 (March) 1937.

Complete case histories of two patients with hypothyroidism are given. The patients were followed while under treatment from 4 to 18 years of age and from 2 to 11 years of age, respectively. Both children when first seen had the appearance and build characteristics of thyroid deficiency and significant retardation in height, bony development and mental development. In both cases complete restitution of osseous development occurred under treatment. The older child acquired a nicely proportioned body with a delicate face but remained permanently dwarfed and retarded mentally. Her intellect did not develop beyond the 10½ year level. The younger child retained her thick-set build but compensated completely in height and mentality.

RAUH, Cincinnati.

PROTAMINE INSULIN: ITS USE IN CHILDREN. ALVAH L. NEWCOMB, MARK W. DICK and LOUISE SCHNUTE, J. Pediat. **10**:437 (April) 1937.

On the basis of a study of fourteen hospitalized patients and eighteen ambulatory patients with juvenile diabetes who were treated with protamine insulin, protamine zinc insulin and protamine calcium insulin, Newcomb, Dick and Schnute draw the following conclusions: Patients with mild juvenile diabetes can be treated successfully with a single dose of protamine insulin in the morning. A large dose of protamine insulin and a small dose of regular insulin administered simultaneously in the morning can control severe diabetes in the majority of patients. Protamine zinc insulin produces a normal midnight blood sugar level and a normal fasting blood sugar level in a shorter time than protamine insulin.

The children studied suffered less from hunger and were more active and alert when given protamine insulin than when regular insulin was used, and those who were able to take all the insulin in the morning, were happier and more stable emotionally than those who took it in divided doses. In twenty-three of the thirty two patients the diabetes was satisfactorily controlled with one matutinal dose of protamine insulin only.

RAUH, Cincinnati.

CLINICAL EXPERIENCE WITH PROTAMINE AND CRYSTALLINE INSULIN IN THE TREATMENT OF DIABETES MELLITUS IN CHILDREN. WALDO E. NELSON and CLYDE DUMMER, J. Pediat. **10**:446 (April) 1937.

This is a report on the treatment of infantile diabetes with protamine zinc insulin. It has been the experience of Nelson and Dummer that it is the exception rather than the rule that diabetic children can be maintained in glycemic equilibrium on one injection of protamine insulin alone. They use the method of Wilder and his associates, which consists of the administration of a single dose of protamine insulin, but in addition they give an injection of regular insulin at the same time in a different site. The initial dose of protamine insulin is administered at night, so that the blood sugar level the following morning is within normal range and the slowly acting protamine insulin does not have to overcome the additional burden of an existing hyperglycemia.

Nelson and Dummer investigated the best time for the injection of the protamine insulin, and with the possible exception of 6 a. m. no advantage was found in giving the injection at any time other than before breakfast. Hypoglycemic shock did occur, most frequently from twelve to twenty-four hours after injection. Because of the prolonged effect of protamine insulin, two and even three hypoglycemic reactions may follow one injection. Crystalline insulin was used in a few cases, and the results did not indicate a sufficient advantage over that of regular insulin to warrant its general use at the present time. The authors feel it is worthy of further trial.

RAUH, Cincinnati.

PROGESTIN AND ESTRIN OF NINETEEN PLACENTAS FROM NORMAL AND TOXEMIC CASES. G. V. S. SMITH and J. H. KENNARD, Proc. Soc. Exper. Biol. & Med. **36**:508 (May) 1937.

Alcoholic extracts were made of placentas obtained from normal pregnant women and women suffering from late toxemia and injected into rats. There was slightly less progestin in the presence of toxemia, but the results are only suggestive. The average figures for placental estrogen show a tendency for values in cases of toxemia to be low, which confirmed previous findings of the authors (Smith, G. V., and Smith, O. W.: *Am. J. Obst. & Gynec.* **33**:365, 1937).

HANSEN, Minneapolis.

THYMUS AND PINEAL GLANDS. SAMSON WRIGHT, Brit. M. J. **1**:874 (April 24) 1937.

This is one of a series of articles on endocrinology. Although the article is brief and might well be abstracted, it must be read in its entirety to be appreciated.

ROYSTER, University, Va.

PATHOLOGY OF THE ADRENAL GLAND IN RELATION TO SUDDEN DEATH. C. K. SIMPSON, Lancet **1**:851 (April 10) 1937.

Simpson briefly reviews present knowledge of the developmental anatomy and physiology of the adrenal glands and then takes up the matter of their pathologic anatomy. The three morbid processes commonly seen are: hemorrhagic necrosis or hemorrhagic infarction, acute caseative tuberculosis and rapid metastatic growth in the gland.

"Although the loss of sodium and its attendant imbalance of electrolytes are the most striking of the processes developing in acute adrenal insufficiency, the clinical features are not adequately explained by this succession of changes alone. It is clear that both hypoglycemia and dehydration have their parts to play; their importance in the mechanism of death cannot be ignored.

"Each of these three biochemical anomalies developed in relation to cortical insufficiency has its experimental champion, Loeb supporting the changes in sodium metabolism, Britton emphasizing the undeniable importance of hypoglycemia, and Swingle and Pfiffner investing the loss of tissue fluid and plasma volume with chief responsibility. Each has claims which are irrefutable, and it is abundantly clear that all three collectively, rather than individually, are to be held responsible for death."

LANGMANN, New York.

CUTANEOUS DYSTROPHY AND OBESITY OF ADRENAL ORIGIN. M. ACQUA, Med. inf. **8**:148 (May) 1937.

Acqua reports the case of a boy of 8 years who showed an area of cutaneous dystrophy about the mouth; there were associated desquamation, scars and erythema. At first congenital syphilis was suspected, but treatment with mercury and arsphenamine did not relieve the condition. The child also was somewhat lethargic, had small genitalia and obesity, the latter especially marked around the breast and gluteal region. Treatment with thyroid gland was tried and resulted in diminution of the obesity and some improvement in mental reaction; but the cutaneous condition was not affected. Acqua felt that the dysfunction probably was not primarily related to the thyroid but rather to the adrenal glands. Both the adrenal cortex and the medulla were believed to be involved. To the cortical disturbance was attributed the thyroid dysfunction and to the medullary was ascribed a dyscrasia of the sympathetic nervous system which included sialorrhea. The sialorrhea was believed responsible for the lesions of the skin. The administration of an extract of whole adrenal gland resulted in the overcoming of the abnormalities reported.

HIGGINS, Boston.

THE RESTORATION OF MUSCLE GLYCOGEN IN THE HYPOPHYSECTOMIZED FROG. R. G. DAMBROSI, Rev. Soc. argent. de biol. **13**:27 (April) 1937.

Dambrosi arrives at the following conclusions: 1. The hypophysectomized frog has less muscle glycogen than the normal frog. 2. Muscle glycogen consumed during prolonged tetanization is not restored in a hypophysectomized frog. 3. A hypophysectomized frog which has received implantations of hypophysis is capable of restoring muscle glycogen following fatigue induced by tetanization. 4. Injections of insulin accentuate the reduction of muscle glycogen in hypophysectomized frogs. 5. In its relationship to muscle glycogen, hypophysial insufficiency is more serious in the frog than in the dog. In the latter, serious effects are not observed or are minimal.

KALISKI, San Antonio, Texas.

ACTION OF HYPOPHYSIAL EXTRACTS AND OF THYROXIN ON HEREDITARY HYPOPHYSIAL INFANTILISM IN MICE. T. KEMP and L. MARX, Acta path. et microbiol. Scandinav. **14**:197, 1937.

This is a continuation of a previous report in which the development of the dwarfed mouse was described. The anterior lobe of the hypophysis of the dwarfed mouse was hypoplastic, and the eosinophilic cells were few or absent. The thymus was smaller than in the normal animal. It became hyperplastic after brief administration of the growth hormone, the lactogenic hormone and the thyrotropic hormone of the hypophysis and of thyroxin, but hyperplasia ceased if treatment continued. The thyroid was equally hypoplastic. The growth hormone caused increase of growth; the action of the thyrotropic hormone was not constant. The growth hormone stimulated the growth of the parathyroids. The medulla of the

adrenal was normal, but the cortex was not fully developed in the untreated animal. The growth hormone caused hypertrophy of the medulla and still further thinning of the cortex. Administration of the growth hormone with thyroxin stimulated normal growth of the cortex. The pancreas showed progressive rapid atrophy, and this was prevented by administration of the growth hormone and thyroxin, the former stimulating the development of the islands and the thyroxin causing their decrease. The growth of the whole animal was greatly influenced by the growth hormone, and normal size was reached after a period of treatment of from two to three months. The sexual functions in the male animals became normal, but those in the females were less influenced. The action of the other hormones was evident but not so striking when each was given alone; when they were combined with the growth hormone the gain of weight was greatest.

DAVIDSOHN, Chicago. [ARCH. PATH.]

HIRSUTISM. L. MEYLER and H. HOMMES, Nederl. tijdschr. v. geneesk. **81**:1701 (April 17) 1937.

Meyler and Hommes describe a case of hirsutism in a young girl presenting all the typical features of the clinical picture. There were excessive growth of hair and adipositas. The child looked much too old for her age, especially her face. Though 11 years of age, she was estimated by several persons, when seen lying in bed, to be 20. The muscular force was considerable; the voice was very deep, and the clitoris was enlarged. She was treated with large doses of an estrogenic preparation. After a period of over one year the girl had assumed a normal appearance; the muscular strength had decreased; the voice had a higher pitch, and the clitoris had become normal. It is pointed out that the syndrome called by most authors hirsutism is due to a hyperfunction of the adrenal cortex. This hyperfunction may have various causes; it is found, for example, in Cushing's disease. The latter name, however, should be reserved for those forms of hirsutism in which the adrenal hyperfunction is brought about by the hypophysis.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Muscles, Bones, Joints and Lymph Glands

OSTEOMYELITIS OF THE SKULL OF OTITIC AND PARANASAL SINUS ORIGIN. H. C. BEHRENS, Arch. Otolaryng. **25**:272 (March) 1937.

The author presents seven cases and shows from the conclusions based on these cases and data from the literature that in the majority of cases osteomyelitis of the skull follows surgical intervention. Its insidious onset is stressed. One should never operate on sinuses unless the indications are definite. The use of the raspatory or the curet should be avoided. Classification of the condition into the localized, self-limited or progressive type should be made as soon as possible, thus making early and appropriate treatment possible. Immunotransfusions should be given repeatedly and adequate surgical treatment should be instituted. Regeneration of bone in cranial defects may take several years. GREENWOOD, Chicago.

ACUTE HEMATOGENOUS OSTEOMYELITIS. A. O. WILENSKY, Arch. Surg. **34**:320 (Feb.) 1937.

Acute hematogenous osteomyelitis is basically composed of two components: a general bacterial infection and a local lesion in the bone tissue. The most important item is the general infection. A number of cases are described which illustrate the various clinical groupings into which cases of acute hematogenous osteomyelitis can be placed. The course and the type of treatment employed in these cases show that treatment for this condition cannot be standardized. The author showed that urgency in operative treatment was usually unnecessary, which is contrary

to the usual opinion. In some of the reported cases operation was unnecessary, but when it was necessary it was limited to the simplest of procedures, frequently to mere incision and drainage of an abscess. The report stresses the fact that acute hematogenous osteomyelitis is an incident in a general bacterial infection.

KAISER, Rochester, N. Y.

PERTHES' DISEASE. C. J. SUTRO and M. M. POMERANZ, Arch. Surg. **34**:360 (Feb.) 1937.

A detailed study of fifty-seven cases of Perthes' disease is reported. Clinical statistics are listed, and the roentgenographic appearances are interpreted in the light of modern pathology. The differential diagnostic factors are discussed. No new ideas are offered, as for the etiology of Perthes' disease.

KAISER, Rochester, N. Y.

OBSERVATIONS ON THE FREI TEST. W. H. CONNOR, E. A. LEVIN and E. E. ECKER, J. Infect. Dis. **60**:62 (Jan.-Feb.) 1937.

These authors demonstrate that the Frei test appears to be specific for lymphogranuloma venereum.

TOOMEY, Cleveland.

PROGRESSIVE FACIAL HEMIATROPHY: REPORT OF TWO CASES WITH CEREBRAL CALCIFICATION. KATHERINE K. MERRITT, HAROLD K. FABER and HILDE BRUCH, J. Pediat. **10**:374 (March) 1937.

Two cases in which progressive facial hemiatrophy and cerebral calcification occurred together are reported in a girl aged 12 years and a boy aged 15 years. The authors believe that this is the first report of a case in which these two lesions were associated. The outstanding features in the first case were: recurring generalized convulsions since the age of 3 years; sclerodermal tissue forming a groove from the right side of the nose to the forehead and another streak beginning in front of the right ear and extending over the right cheek; hemiatrophy of the right side of the face; subnormal mentality, and multiple areas of intracranial calcification in the right posteroparietal region.

In the second case there was a history of trauma to the head and forehead; some time later, at the age of 4 years, generalized convulsions began. At this time a pigmented scar was noted over the right forehead, extending from the hair line to the inner end of the right eyebrow. A year later asymmetry of the face was noted, the right side appearing smaller than the left. The roentgenogram of the skull showed calcification in the occipital region just to the right of the midline.

The authors give brief abstracts of the histories of the patients since 1930 and discuss the theories of the pathogenesis and etiology of the disease. Archambault and Fromm expressed the belief that progressive facial hemiatrophy is a well defined symptom complex. The various lesions described involve the sympathetic division of the vegetative nervous system at some point in either its central or its peripheral course. They stated that though the etiology is still obscure, frequent antecedent infections or trauma to the face or neck may be the exciting cause.

The atrophic process may involve all the structures of the face, and involvement of the bone is inversely proportional to the age at which the hemiatrophy has its onset. The connection between progressive facial hemiatrophy and scleroderma is still far from solution. Pigmentary anomalies are often present in this disease.

Of 400 cases of progressive facial hemiatrophy reported, convulsions occurred in 11. Archambault and Fromm were of the opinion that this incidence is purely coincidental, but the authors believe that the percentage is too high to be so. In the first case in this report the convulsions occurred from three to four years before appearance of the facial hemiatrophy. The authors concluded that the

convulsions in this case were directly related to the cerebral calcification. In the second case the convulsions were probably related to a cerebral lesion which later became calcified. They believe that the cerebral lesions in their patients conform most closely to calcified hemangioma. They are unable to determine the relationship of the intracranial process to the hemiatrophy in either case.

RAUH, Cincinnati.

EARLY DIAGNOSIS OF CONGENITAL PRELUXATION OF THE HIP. M. ORTOLANI, Pediatria **45**:129 (Feb.) 1937.

Ortolani calls attention to a sign not so well known in the diagnosis of congenital preluxation of the hip. This sign is marked by a sensation of a sudden jerk felt by the examining hand or even visible to the naked eye when the patient is lying in a recumbent position with knees flexed and somewhat abducted. It is usually elicited by suddenly abducting the limb with slight external rotation. It is usually present about the third month of life and persists up to the twelfth month. It is found in 60 per cent of the cases and is a positive index of articular deformity of the hip, of the preluxation type.

PALMIERI, Brooklyn.

MYASTHENIA GRAVIS IN A CHILD THREE AND A HALF YEARS OLD. L. TARANTO, Pediatria **45**:137 (Feb.) 1937.

Taranto describes a myasthenic syndrome associated with acute hypo-adrenalism in a child 3½ years old who had been complaining for a year of bouts of fever, the nature of which had not been ascertained (malaria).

Taranto's opinion is that the endocrine theory seems to be the most logical one to explain myasthenia gravis, and he based this on the anamnestic data, on clinical study and on the results that he obtained with this therapy. Capsular extract of adrenal was given by intramuscular injection daily.

PALMIERI, Brooklyn.

CHRONIC RHEUMATISM OF THE DEFORMING TYPE SECONDARY TO ACUTE ARTICULAR RHEUMATISM. A. RENZULLI, Pediatria **45**:143 (Feb.) 1937.

A patient 11 years old was seized with pains in the different joints of the body and a high fever. Rest in bed and plenty of salicylates had no appreciable effect. After one month of fever, the pain disappeared from most of the joints, but these remained in the stage of tumefaction and ankylosed. Different treatments were used for a period of three years, but all proved futile. The patient lost even the power of locomotion because of rigidity of the spinal column. In favor of his diagnosis Renzulli takes into consideration the clinical history and course, the absence of symptoms that might speak for other forms of chronic arthritis, the lack of familial incidence, the absence in the patient and parents of glandular disturbances, especially of the thyroid gland, and the physical development of the child, which rules out chronic articular rheumatism of the endocrine type. Moreover, he takes into consideration the absence of the triad present in Still's disease and the tubercular form of rheumatism described by Poncet. Wagner and Cattaneo, of the Eschenich clinic, reported few cases in many thousands of children who were examined by them. Renzulli has seen since 1926 only eight cases. Honkeimer has suggested a better name for chronic forms of rheumatism of the primary type; he uses "arthritis chronica deformans juvenilis," reserving "chronic articular rheumatism" to designate the condition secondary to acute articular rheumatism. Renzulli concludes by stating that chronic articular rheumatism of the deforming type is long and progressive in course and leads to serious lesions. The prognosis is always grave.

PALMIERI, Brooklyn.

PAGET'S DISEASE IN A CHILD. SCHEURLEN, Kinderärztl. Praxis **8**:56 (Feb.) 1937.

This is a description of Paget's disease seen in a girl 11 years of age. The disease was associated with albuminuria and a disturbance in water metabolism suggestive of diabetes insipidus. HEYMANN, Cleveland.

CONCERNING MARBLE BONE DISEASE. G. O. HARNAPP, Monatschr. f. Kinderh. **69**:1 (Feb.) 1937.

This is an interesting study of a family in which eleven members showed a high grade diffuse osteosclerosis without any manifestations of metabolic disturbance. There are twelve illustrations, including x-ray pictures, of the bony structures of the skull, ribs and long bones. There were few symptoms, the disease being found on examination of x-ray pictures of one patient and the others being then examined in routine fashion. The x-ray pictures showed the typical marble-like appearance of the bones.

Large doses of vitamin D had no effect, while doses of parathyroid higher than the average led to retention of calcium.

The plasma phosphatase was definitely increased.

The absence of symptoms in these children was in sharp contrast to the usual picture of this marble bone disease. Harnapp suggests classifying the osteoscleroses into three groups: (1) malignant osteosclerosis with anemia (Albers-Schoenberg), (2) malignant osteosclerosis without anemia and (3) benign, familial osteosclerosis.

GERSTLEY, Chicago.

GENERALIZED RHEUMATIC CHONDROMALACIA. F. ALTHERR, Virchows Arch. f. path. Anat. **297**:445, 1936.

This paper gives a detailed study and discussion of a unique case. A boy of 14 years nine months before his death became ill with acute tonsillitis. This was followed by nonpurulent febrile polyarthritis. Softening of the laryngeal cartilages and collapse of the larynx and trachea necessitated tracheotomy. The cartilage of the nose and ears also became softened. Death was due to generalized miliary tuberculosis, which had its origin in a fresh caseous lesion of the upper lobe of one lung. Necropsy revealed marked softening of all the cartilaginous tissues of the body. In the periarticular tissues there was observed the fibrinoid degeneration of early active rheumatic disease, and in the myocardium, Aschoff bodies (rheumatic granulomas). The cartilaginous tissues revealed a combination of degenerative, resorptive and inflammatory changes. The degenerative changes consisted in fibrinoid swelling, hyalinization, asbestos-like degeneration and splitting of the ground substance, and disappearance of cartilage cells. Resorption of degeneration products occurred by means of an inflammatory granulation tissue which invaded the cartilage from the surrounding perichondrium or joint capsule. Localized small areas of new formation of cartilage and bone were seen. The author concludes that the generalized disease of the cartilaginous system was part of the rheumatic process, the widespread involvement of the cartilage having perhaps a constitutional basis. SCHULTZ, Evanston, Ill. [ARCH. PATH.]

PUNCTATE EPIPHYSIAL DYSPLASIA. C. DE LANGE, Maandschr. v. kindergeneesk. **6**:179 (Feb.) 1937.

Attention is drawn to the mottled appearance of the epiphyses at the roentgenologic examination. This aspect is probably due to insufficient development. In the rare cases reported there was mostly a question of a peculiar form of chondrodystrophia. However, in the case of Buxton (1930) and in the author's case this disease was absent, whereas in the author's case there also existed peculiar atrophy of the metaphyses. VAN CREVELD, Amsterdam, Netherlands.

THE "RESILIENT FINGER" IN YOUNG CHILDREN. R. J. HARRENSTEIN, Nederl. tijdschr. v. geneesk. **81**:1237 (March 20) 1937.

After a brief review of the symptoms of "resilient finger" in adults attention is drawn to this condition in the thumb, which is not infrequent in early childhood. As conservative treatment in some of these cases proves unsuccessful, a number of children had to be submitted to operation. A cartilaginous thickening of the tendon could be demonstrated as the underlying cause in two cases.

VAN CREVELD, Amsterdam, Netherlands.

MORBUS PANNER. P. M. E. E. NYST, Nederl. tijdschr. v. geneesk. **81**:1243 (March 20) 1937.

The author describes the case of a boy of 8 years who had aseptic necrosis of the capitulum humeri, a condition extensively described by Panner.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Eye

LYMPHOSARCOMA OF EYELID. V. M. MÉTIVIER, Brit. J. Ophth. **21**:202 (April) 1937.

Sarcoma of the eyelid is a rare growth, but Smith and Elmes in an analysis of five hundred tumors among the natives of Nigeria found ten cases of round cell sarcoma of the orbit. These authors suggested that probably many of these growths had their origin in trauma, since injuries to the eyes are notably common among natives.

Métivier reports a case of lymphosarcoma of the eyelid. The patient was a brown-skinned boy of impure African descent living in Trinidad. When he was first seen the condition appeared to be a large untreated chalazion. Antisyphilitic treatment was given, as the Wassermann reaction was strongly positive. No effect was noted from the treatment, and as the growth at that time completely hid the globe and there was an extension toward the subconjunctival tissue of the lower lid, with invasion of the caruncle and plica, exenteration of the orbit, with removal of the eyelids, was done. Histologic examination proved the growth to be a large round cell sarcoma. An enlarged lymph node on the angle of the jaw showed the same structure. Two years later there was no evidence of recurrence, and the patient was in good health.

This article is illustrated. ZENTMAYER, Philadelphia. [ARCH. OPHTH.]

OPHTHALMIC HERPES ZOSTER. H. JATOBA, Pediat. e puericultura **5**:48 (March) 1937.

The various treatments for ophthalmic herpes zoster are discussed. The author favors the use of local applications and analgesics. SANFORD, Chicago.

HEREDITARY DEVELOPMENTAL ERRORS AS CAUSE OF LOWERED RESISTANCE. W. LÖHLEIN, Arch. f. Ophth. **136**:434 (Feb.) 1937.

The assumption that eyes with hereditary developmental errors are predisposed and less resistant to inflammatory or degenerative diseases acquired intra vitam is illustrated with three instructive but hardly conclusive reports of cases.

P. C. KRONFELD. [ARCH. OPHTH.]

Skin Diseases; Allergy

ACRODYNIA. R. L. NELSON, Arch. Pediat. **54**:300 (May) 1937.

Nelson reports what he considers to be a fatal case of acrodynia in a 4 month old breast-fed infant. ORR, Buffalo.

ATTEMPT TO PRODUCE THE ATOPIC INHIBITOR ANTIBODY IN NONATOPIC INDIVIDUALS. M. R. LICHTENSTEIN, J. Allergy **8**:228 (March) 1937.

Two nonatopic persons were given twelve intravenous injections of 1 per cent extract of ragweed in doses of from 0.1 to 0.5 cc. over a period of six weeks. Serum was prepared from blood withdrawn a week later and tested in several ways. The author concludes from the results obtained that an atopic inhibitor antibody could not be demonstrated.

HOYER, Cincinnati.

HEMATOLOGIC RESPONSE IN FOOD ALLERGY EOSINOPHILIA IN THE LEUCOPENIC INDEX. T. L. SQUIER and F. W. MADISON, J. Allergy **8**:250 (March) 1937.

Three preliminary counts were made at fifteen minute intervals and fifteen, thirty, sixty and ninety minutes after ingestion of the test food. The counts were made in the usual counting chamber, and the Camara and Alvarez modification of the acetone-eosin diluting fluid was used. This allows for simultaneous counting of eosinophils and leukocytes.

The 200 tests were performed on eighty-four allergic patients, all of whom showed negative or doubtful reactions to cutaneous tests with the foods ingested. The hematologic response was positive in 102 of the tests, doubtful in 4 and negative in 94.

There is a definite correlation between the increase in eosinophils and the increase in leukocytes which result. In a few instances there was a definite increase in the eosinophils when the leukopenia was doubtful. The eosinophil count is at its peak at the thirty minute interval. It differs from the leukocyte count in that it does not return to the initial level until after the ninety minute interval.

The authors feel that the hematologic response is an aid to diagnosis and should be used only to supplement the usual method of skin testing.

HOYER, Cincinnati.

ARACHIDONIC AND LINOLIC ACID OF THE SERUM IN NORMAL AND ECZEMATOUS HUMAN SUBJECTS. W. R. BROWN and A. E. HANSEN, Proc. Soc. Exper. Biol. & Med. **36**:113 (March) 1937.

Linolic acid (tetrabromides calculated as such) is present in human serum to the extent of about 5 per cent of the total fatty acids, and arachidonic acid (polybromides calculated as such), in about 3 per cent of the total fatty acids in pooled samples of the blood serum of normal children. The content of both these fatty acids is definitely diminished in children with eczema. In the patients with active eczema who were clinically cured either by the internal administration of oils rich in the unsaturated fatty acids or by the local application of ointments containing crude coal tar or both, the arachidonic acid content of the serum was not increased, while the linolic acid content was the same as that found in normal subjects. These findings indicate a possible reason for the low iodine number of the fatty acids of the serum in cases of eczema and further suggest that a disturbance in the metabolism of the unsaturated fatty acids may be one of the many factors at fault in this condition.

HANSEN, Minneapolis.

INHERITANCE OF ALLERGIC DISEASE. A. S. WIENER, I. ZIEVE and J. H. FRIES, Ann. Eugenics **7**:141, 1936.

As the authors of this article point out, there seems to be no unanimity of opinion as to the mode of transmission of allergic disease. According to Cooke and Vander Veer and Spain and Cooke, allergy is transmitted as a simple mendelian dominant. In direct contrast, Adkinson maintains that her findings favor a recessive mechanism. Furthermore, Richards and Balyeat suggest that the condition is inherited as a "partial dominant." An analysis of the authors' studies

of 66 complete families with 250 children, as well as of data already published, failed to support either the simple dominant or the recessive theory. The theory that allergy is transmitted as a simple mendelian dominant does not explain why more than half the pedigrees of both parents are normal. The theory that the mechanism is recessive is refuted by the existence of pedigrees of families in which both parents are affected yet some of the children are normal. The authors present for consideration a new theory of heredity of allergic disease. According to this theory, allergic disease is transmitted by means of a single pair of allelomorphic genes, *H* and *h*, with *h* determining allergy and *H* representing the contrasting normal gene. Three different genotypes are possible:

1. Genotype *HH*—pure normal.

2. Genotype *hh*—pure allergic. Persons of this genotype show symptoms of allergic disease before the age of 10 years.

3. Genotype *Hh*. The majority of persons of this type remain apparently normal throughout life, although they transmit the abnormal gene *h*. The rest, depending on environmental conditions, will manifest allergic diseases, but the symptoms will not appear until after puberty. The existence of two sorts of allergic persons is supported by the bimodal distribution when cases are classified according to the age of the patient at the time of onset. Moreover, statistical analysis of the authors' own findings in studies of families and of data previously published lends additional support to the theory. One finding that remains to be explained is the excess of males over females among those in whom allergic disease develops before puberty.

WIENER, Brooklyn. [ARCH. PATH.]

HEREDITARY SEBACEOUS CYSTS. J. T. INGRAM and MICHAEL C. OLDFIELD, Brit. M. J. **1**:960 (May 8) 1937.

A discussion of sebaceous cysts is furnished, together with statements of the several theories. Two cases are discussed in detail and several others mentioned briefly. Other members of the family of the two patients are mentioned, including those with cysts, acne and other cutaneous lesions. A family tree, showing apparent genetic tendencies, is exhibited. The condition is discussed and summarized as follows: A family presenting multiple hereditary sebaceous cysts is described. Cases of this type throw light on the etiology of the common sebaceous cyst. The evidence against the widely accepted theory of retention is discussed.

ROYSTER, University, Va.

EPIDEMIOLOGY OF EPIDEMIC DROPSY. R. B. LAL and S. C. ROY, Brit. M. J. **1**:1110 (May 29) 1937.

A discussion of this obscure disease is given, with various observations and special reference to the examination of theories, including the rice theory, the contagion theory and the mustard oil theory. Certain experiments were made on human volunteers, and a brief discussion of these experiments is given. The summary of the study is as follows:

1. A brief statement is given of the results of epidemiologic studies in connection with outbreaks of epidemic dropsy in seven localities in Bihar, Bengal, Assam and Orissa, India, representing rural, semirural, urban and industrial conditions.

2. An epidemiologic experiment designed to test the contagiousness of the disease in a semi-isolated community is described briefly.

3. Three principal theories of the etiology of the disease are discussed, and it is shown that the facts observed fail to support the diseased rice and the contagion theory. A satisfactory explanation of these facts is provided by the hypothesis that epidemic dropsy as commonly seen in these provinces is caused by a deleterious substance contained in certain consignments of mustard oil.

4. Experiments on human subjects, living under strictly controlled conditions, are described. They show that signs and symptoms of epidemic dropsy are produced in healthy young men by giving them food cooked in a brand of mustard oil which is strongly suspected, on epidemiologic grounds, of being responsible for an epidemic—the "diseased" rice having been altogether excluded from the experimental food.

5. Practical application of these findings is discussed.

ROYSTER, University, Va.

THE VEGETATIVE NERVOUS SYSTEM IN SCLERODERMA. J. RUSSETZKI, Gaz. d. hôp. **110**:381 (March 24) 1937.

The author has found that in scleroderma during the stage of edema the involved areas show an altered dermatographia and that in the second (vasodilatation) phase this phenomenon is diminished. In the atrophic stage only white dermographia is obtained, and the pilomotor reaction is diminished also. The oculocardiac reflex remains normal.

KAJDI, Baltimore.

PATHOGENESIS OF ERYTHEMA NODOSUM. C. DEMURTAS, Med. inf. **8**:134 (May) 1937.

There are four opinions as to the pathogenesis of erythema nodosum. 1. It is a disease of itself like the other exanthems of childhood. 2. It is a clinical manifestation of rheumatic fever. 3. It is related to tuberculosis, being either the result of a direct action of the tubercle bacillus or a manifestation of allergy to tuberculin. 4. It is a syndrome found in association with various infections, as tuberculosis, syphilis, acute arthritis, pneumococcemia or gonococcemia.

An epidemic occurred in a boarding school which led Demurtas to believe that tuberculosis is definitely the cause of the condition. One boy, aged 15, contracted acute pulmonary tuberculosis with cavity formation and died. Three other students who roomed with him came down with erythema nodosum. One of these students had tracheobronchial adenitis; a second, pleurisy with effusion, and the third, probable pulmonary tuberculosis. Each of these children showed a positive reaction to tuberculin. None of the other children in the school had erythema nodosum.

HIGGINS, Boston.

A CASE OF "CUTIS LAXA IPO-ELASTICA." A. SETTI, Lattante **8**:342 (May) 1937.

A child of 6 months had practically from birth a skin which was hypo-elastic and wrinkled. The skin was soft and slightly greasy. The child was under par physically and mentally. A possible etiology for the condition is suggested from the fact that the parents were cousins and not in particularly robust health. Setti believes that "cutis laxa ipo-elastica" represents a recessive hereditary factor.

HIGGINS, Boston.

Miscellaneous

SULPHEMOGLOBINEMIA AND METHEMOGLOBINEMIA FOLLOWING ADMINISTRATION OF P-AMINOBENZENE SULPHONAMIDE. J. P. J. PATON and J. C. EATON, Lancet **1**:1159 (May 15) 1937.

Administration of magnesium sulfate simultaneously with, or within two or three days preceding, administration of sulfanilamide gives rise in most persons to sulfhemoglobinemia. The formation of sulfhemoglobin takes place very rapidly even after small doses of the drug.

In the absence of sulfates large doses of the drug are well tolerated, but in a considerable proportion of persons doses of from 12 to 24 Gm. per diem result in methemoglobinemia.

The removal of sulfhemoglobin from the blood is much slower than the removal of methemoglobin. The former has been detected six weeks after the administration of sulfanilamide ceased. The latter disappears in approximately twenty-four hours.

LANGMANN, New York.

RECURRENT ABDOMINAL PAIN IN CHILDHOOD. L. MALE, M. J. Australia **1**:782 (May 22) 1937.

This paper omits discussion of all acute abdominal conditions in children and simply reviews the possibilities suggested in recurrent abdominal pain ranging from tuberculosis of the spine, through intestinal parasites, abdominal adenitis, tuberculous peritonitis, cyclic vomiting, etc. He warns against blaming psychic causes and also against blaming constipation for recurrent abdominal distress.

TENNEY, Madison, Wis.

PEDIATRICS: REVIEW OF RECENT LITERATURE. H. HORSTERS, Med. Klin. **33**:514 (April 9) 1937.

Since the article itself consists of abstracts of forty recent publications, it does not lend itself well to abstracting.

SIEMSEN, Chicago.

INFECTIONS CAUSED BY INJECTIONS OF MATERNAL BLOOD. LAJOS HANNY, Monatschr. f. Kinderh. **70**:101 (April) 1937.

Two cases are reported in which infections developed after an injection of maternal blood. A 7 year old girl was given an inoculation of 45 cc. of her mother's blood for treatment of an asthmatic bronchitis. Several hours later the picture changed to one of diffuse bronchopneumonia. The mother was well when the blood was taken but sickened that evening with symptoms of grip. Evidently her blood harbored the organisms.

A 1 year old child received an injection of 40 cc. of her mother's blood as a preventive against a prevalent epidemic of measles. Coincidentally the mother sickened with measles. The disease did not develop in the child.

GERSTLEY, Chicago.

AN UNUSUAL CASE OF OPIUM POISONING IN CHILDHOOD. T. F. SU and H. S. YANG, Chinese M. J. **51**:549 (April) 1937.

Poisoning from the external application of opium is rare at all times of life. Su and Yang report an instance in a 6 year old boy whose chest had been scalded with hot water and soon thereafter a diluted opium paste containing 10 Gm. of the drug had been applied over the wound. Within sixty minutes the child was unconscious. The rectal temperature rose to 40 C. (104 F.), the pupils became contracted and the conjunctival reflex disappeared. The respiratory rate was 18 per minute but was normal in type, and the lungs were full of moist rales. The percentage of polymorphonuclears in the blood was 93. The urine remained normal. On the third day irregular breathing developed, and death soon followed. The extensive area of absorption was apparently a factor. Children are probably more susceptible to opium at a time of life when the respiratory center is not completely developed. Ten grams of opium represent 1 grain (0.065 Gm.) of morphine. If this is only partly absorbed in a child of this age, the overwhelming depressant action will produce death. Su and Yang do not mention the possible influence of the burn on the fatal outcome.

NEFF, Kansas City, Mo.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

Regular Meeting, Oct. 19, 1937

C. A. ALDRICH, M.D., *President*

GEORGE F. MUNNS, M.D., *Secretary*

THE PROBLEM OF CROSS-INFECTIONS IN AN INFANT'S AND CHILDREN'S HOSPITAL. DR. C. F. MCKHANN (by invitation) Harvard University Medical School, Boston.

The problem of hospital infections in an infants' hospital is at present a question not so much of control of gastro-intestinal and of so-called contagious diseases as of prevention of acute respiratory infections and of certain skin ailments.

Duration of hospitalization was found to influence greatly the incidence of infections from which premature, malnourished and chronically ill infants suffered most. Patients with eczema, cerebral deficiency and congenital anomalies also represented bad hospital risks. Infants who had been well up to the development of the acute conditions which led to hospitalization suffered little from secondary infections.

The present analysis, in accord with results in the literature, indicates that despite great progress in the betterment of precautions in regard to isolation there may still be major flaws in the technic of isolation in institutions caring for infants.

The clinical observations on the possibility of air transmission of measles, chickenpox and acute respiratory infections in the light of the work of Wells, Hart and others indicates that air-borne infection may play a larger rôle than is generally recognized.

From my experience and from a review of the literature certain procedures and directional efforts may be derived:

1. Hospitalization of infants should be employed only when necessary, and no infant should be kept in the hospital longer than his condition demands.

2. The susceptibility of premature, malnourished and chronically ill, eczematous, syphilitic or mentally defective children to acute infections raises grave question as to the wisdom of placing such patients in wards with acutely ill infants or having them cared for by nurses who are also attending infants with acute infectious diseases, notably respiratory and cutaneous infections.

3. In any hospital ward caring for infants each patient should be in a separate cubicle. Open cubicles, with walls not reaching to the ceiling, are less satisfactory than cubicles with walls extending to the ceiling; these in turn are less effective than separate rooms with individual outside ventilation.

4. The efficacy of ultraviolet light for sterilizing the air of wards should be subjected to more extensive trial.

5. Adequate masks of a filtering or deflecting type should be worn by all attendants. The usual gauze mask is not adequate. Under certain conditions, gauze masks with cotton fillers or masks of paper or of cellophane are adequate.

DISCUSSION

DR. MAURICE L. BLATT: Dr. McKhann has advanced the knowledge of cross-infection and presented a convincing and interesting report of his research. His experience with the use of the ultraviolet ray as a bactericidal agent in medical wards offers a method of control of cross-infection that is most promising.

To prevent cross-infection in institutions is not simple. Aseptic nursing would prevent much of it but is dependent on a fixed nursing and medical personnel. This is not compatible with education of nursing and medical students and is costly.

The plan I have found practicable and workable is based on the following general rules:

1. Careful examination of admitted patients for evidence of contagious disease, onset of disease or convalescence from it.

2. Careful taking of the history as to recent contact of the admitted patient with contagious disease.

3. Making of vaginal smears for the gonococcus and of nose and throat cultures for Streptococcus haemolyticus and Corynebacterium diphtheriae.

4. Intramuscular injection of whole blood from parents or of normal human serum from the pooled stock on admission.

5. Individual isolation for forty-eight hours.

6. When infection occurs in a ward, it is limited to that ward, and cultures are taken and skin tests are made on the nursing and medical personnel as well as on patients who have been in contact with the infected patients. When indicated, passive immunization with whole blood or specific serum follows.

7. The infectious patient is removed to the hospital for contagious diseases.

8. The carrier in the personnel is removed.

9. No movement of patients who were in direct contact is allowed for two weeks. No patient in my institutions is ever moved from a room where infectious disease occurs to another room. All contacts are considered as incubating the disease for fourteen days or are isolated until specific serum or vaccine has produced immunity.

DR. JOSEPH BRENNEMANN: I want to express my appreciation of this most interesting paper. I think that one is deeply gratified when one's impressions are verified by statistical evidence. There are some things that Dr. McKhann did not touch on as heavily as, I am sure, he feels he should have if there were more time. One of these is the fact that babies should be kept out of the hospital if they can possibly be taken care of as well or better outside. My associates and I have solved that to the extent that during the seasons of the year in which we used to have our 30 bed ward filled we now have sometimes only 6 or 7 patients. Our infant ward is a "double decker" and we put the infectious patients on the lower floor and the noninfectious ones on the upper floor—analogous to the clean and the infectious surgical wards. I heartily agree with what Dr. Blatt has said —that the great danger comes with carriers, by which I mean every person who comes in contact with the child and has some type of infection. Any of our nurses and interns who has a cold or sore throat is taken off the ward, especially the infant ward, until well.

I have still an open mind with reference to masks as long as nurses, interns and physicians in attendance are not expert bacteriologists. In inexperienced hands a mask may be a menace rather than a protection. We have had no experience such as Dr. McKhann has detailed with reference to the use of the ultraviolet ray. It sounds promising. I only hope that we will not find some day that an agent so powerful that it will kill micro-organisms on the fly will be harmful to the patient whom it is used to protect against them.

DR. CLIFFORD GRULEE: I have enjoyed this paper as well as anything I have heard. It represents the type of approach to a subject which is altogether rational and to be approved. There are one or two things, however, I should like to say. One is that no matter what one may have in the way of mechanical devices the ultimate source of trouble will be the personnel, and if the mechanical devices tend to develop carelessness in that personnel their object is defeated. What frequently happens is that one gets some mechanical device that helps greatly, and then after a few years' use a certain carelessness develops, and one slips back. I am not

opposed to anything Dr. McKhann has advocated. I think his study represents an advance, but I hope any such developments will not do away with vigilance in the care of children. That is not alone a matter of careful nursing and of watchfulness on the part of interns and attending physicians, but it is also a matter of getting the children out of the hospital at the earliest possible moment. I am not wholly in accord with Dr. Brennemann regarding home care. What my associates and I have seen happen again and again is that when a child comes in with an infection, we cure it within three or four days and send the child home, only to have it return with an infection which we did not give it but which it got at home. Many children from poorer homes are much safer in the hospital than at home, because when they go back another child may have a cold. That is especially true in the group of debilitated children and premature infants.

Dr. C. F. McKhann: I agree with Dr. Blatt that measles crawls up the wall, and so does chickenpox. Dr. Brennemann is keeping children with infectious diseases on the lower floor, but if he kept those with measles or chickenpox on the lower floor he would soon find these diseases up above.

Acute Laryngotracheobronchitis. Dr. Joseph Brennemann, Dr. Paul H. Holinger and Willie Mae Clifton.

This article will be published in full, with discussion, in a later issue of the American Journal of Diseases of Children.

Book Reviews

Concepts and Problems of Psychotherapy. By Leland E. Hinsie, M.D. Price, $2.75. Pp. 199, with 5 tables. New York: Columbia University Press, 1937.

"The purpose of this book is to indicate the general conceptions that prevail with respect to the structure and functions of the mind, and to show as well as possible what influences these conceptions have had upon the problems of psychotherapy."

The author describes in an extremely clear, impersonal and scientific way the views of the outstanding schools of psychiatry, namely, psychoanalysis (Freud), psychobiology (Mayer), individual psychology (Adler) and analytic psychology (Jung). There are a chapter on the statistical evaluation of psychotherapeutic methods (by Dr. Carney Landis) and a chapter pointing out the nature of psychiatric problems.

In the discussions of the different therapeutic approaches commonly used in psychiatry, the author has given many valuable impressions of the validity and shortcomings of the various schools, showing by direct comparisons their similarities and dissimilarities. Finally, he indicates authoritatively the present state of psychiatric knowledge.

The material is presented in a logical manner and is written in a lucid and interesting style. It summarizes present day psychiatric therapeutic procedure.

Synopsis of Digestive Diseases. By John L. Kantor, Ph.D., M.D. Price, $3.50. Pp. 302, with 40 illustrations. St. Louis: C. V. Mosby Company, 1937.

In this text, a well abbreviated study on digestive diseases is given. The author has drawn from his own clinical and roentgenologic experiences and has extracted the more succinct elements from the literature to compile a handy work dealing with all phases of the pathology of the alimentary tract and with conditions intimately related. He considers generally important laboratory methods used in gastro-enterology, then discusses the diseases of the alimentary tract from the oral cavity downward including the liver, biliary system and pancreas, and concludes with an outline of intestinal parasites. Other diseases causing gastro-intestinal symptoms are mentioned.

The consideration of each disease is well outlined as to definition, etiology, pathology, symptoms, diagnosis and treatment. There are numerous illustrations, diets, charts and statistics to augment descriptions; all done in a brief yet thorough manner.

Mikromethodik. By Ludwig Pincussen. Price, 5 marks. Pp. 193, with 31 illustrations. Vienna: Franz Deuticke, 1937.

The first part of the book discusses the general principles of micromethods and the apparatus used and also colorimetric and nephelometric methods. The second section describes in detail methods for the analysis of urine, including all of the important inorganic and organic constituents. This is followed by a similar section on the analysis of the blood. The methods described are all excellent and are given in much detail. The fourth section is devoted to the determination of the inorganic constituents of tissues. The sections on the analysis of blood gases and the determination of the hydrogen ion concentration follow. The methods discussed throughout the book are well selected and accurately described and are wide enough in scope to cover the needs of clinical laboratory workers. The index is well prepared and accurate.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Professor G. Scheltema, 6a Herreplein, Groningen, Netherlands.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Prof. Luigi Spolverini, Policlinico Lungo Tevere Melini 24, Rome, Italy.
Secretary: Professor Vitetti, Rome, Italy.
Place: Boston. Time: Summer and Fall, 1940.
American Committee:
Chairman: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary: Kenneth Blackfan, 300 Longwood Ave., Boston.
Canadian Committee:
Chairman: Dr. H. B. Cushing, 1390 Sherbrooke St., W., Montreal.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St., W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

British Paediatric Association

President: Dr. J. Wilkie Scott, 40 The Rope Walk, Nottingham, England.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Paediatrický Spolok na Slovensku

President: Dr. A. J. Chura, Lazaretská 6, Bratislava, Czechoslovakia.
Secretary: Dr. S. Limbacher, Dlhá 2, Bratislava, Czechoslovakia.
Place: Pediatric Clinic, University, Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Dr. T. Twistington Higgins, 12 Queen Anne St., London, W. 1.
Secretary: Dr. Reginald Lightwood, 86 Brooke St., London, W. 1.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:30 p. m.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv, Palestine.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv, Palestine.

Sociedad Cubana de Pediatría

President: Prof. Félix Hurtado Galtés, Carlos III 7, Habana.
Secretary: Dr. Carlos Hernández Miyares, San Lazaro 370, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Third Thursday of every month.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

NATIONAL

American Medical Association, Scientific Assembly, Section on Diseases of Children

Chairman: Dr. Clifford D. Sweet, 2940 Summit St., Oakland, Calif.
Secretary: Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester, N. Y.
Place: San Francisco. Time: June 13-17, 1938.

American Academy of Pediatrics

President: Dr. Philip Van Ingen, 125 E. 71st St., New York.
Secretary: Dr. C. G. Grulee, 636 Church St., Evanston, Ill.
Place: Del Monte Hotel, Del Monte, Calif. Time: June 9-11, 1938.
Region I. Place: Rochester, N. Y.
Region III. Place: Detroit, Mich.

American Hospital Association, Children's Hospital Section

Chairman: Miss Mabel Binner, Children's Memorial Hospital, Chicago.
Secretary: Winifred Culbertson, Children's Convalescent Hospital, Cincinnati.

American Pediatric Society

President: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.
Place: The Sagamore, Bolton Landing, New York. Time: June 9-11, 1938.

Canadian Society for the Study of Diseases of Children

President: Dr. Alton Goldbloom, 1543 Crescent St., Montreal, Quebec.
Secretary-Treasurer: Dr. Pearl Summerfeldt, Hospital for Sick Children, Toronto, Ont.

Society for Pediatric Research

President: Dr. Samuel Z. Levine, 525 E. 68th St., New York.
Secretary: Dr. A. A. Weech, 3975 Broadway, New York.

SECTIONAL

North Pacific Pediatric Society

President: Frederick Fischer, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. C. L. Lyons, Paulsen Medical-Dental Bldg., Spokane, Wash.
Place: Seattle. Time: Last Saturday in January 1938.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Gilbert Levy, 20 S. Dunlap St., Memphis, Tenn.
Secretary: Dr. Hughes Kennedy Jr., Highland Plaza Apts., Birmingham, Ala.

STATE

Alabama Pediatric Society

President: Dr. J. H. Baumhauer, 56 St. Joseph St., Mobile.
Secretary-Treasurer: Dr. M. Vaun Adams, 803 Government St., Mobile.
Place: Mobile. Time: Third Monday in April 1938.

Arkansas State Pediatric Association

Chairman: Dr. E. C. McMullen, 500 Main St., Pine Bluff.
Secretary: Dr. Madeline M. Melson, 909 Main St., Little Rock.
Place: Texarkana, Ark. Time: February 1938.

California State Medical Society, Section on Pediatrics

Chairman: Dr. E. Earl Moody, 3780 Wilshire Blvd., Los Angeles.
Secretary: Dr. Hartzel H. Ray, 23—2d Ave., San Mateo.
Place: Pasadena. Time: May 9-12, 1938.

Florida State Pediatric Society

President: Dr. Douglas D. Martin, 442 W. Lafayette St., Tampa.
Secretary: Dr. Warren W. Quillian, 227 Avenue Aragon, Coral Gables.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. Roger W. Dickson, 33 Ponce de Leon Ave., N. E., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.
Place: Augusta. Time: April 1938.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. J. Harold Root, 103 N. Main St., Waterbury.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

Indiana State Pediatric Society

President: Dr. Ernest R. Carlo, 2902 Fairfield Ave., Fort Wayne.
Secretary-Treasurer: Dr. Mathew Winters, 23 E. Ohio St., Indianapolis.
Time: Two meetings a year.

Louisiana State Pediatric Society

President: Dr. Clarence H. Webb, 624 Travis St., Shreveport.
Secretary-Treasurer: Dr. Ruth Aleman, 1407 S. Carrollton Ave., New Orleans.
Place: New Orleans. Time: April 25-27, 1938.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. John D. Craig, 33 E. 61st St., New York.
Secretary: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Place: New York. Time: May 9-12, 1938.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John P. Scott, 1740 Bainbridge St., Philadelphia.
Secretary: Dr. John M. Higgins, 600 S. Wilbur Ave., Sayre.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. C. R. Dengler, 131 W. Michigan Ave., Jackson.
Secretary: Dr. Ward Chadwick, 524 Medical Arts Bldg., Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Secretary-Treasurer: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Place: To be designated by Society. Time: Yearly.

Nebraska Pediatric Society

President: Dr. J. A. Henske, 1614 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. J. H. Murphy, 915 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

North Carolina Pediatric Society

President: Dr. John LaBruce Ward, Arcade Bldg., Asheville.
Secretary: Dr. Lewis Elias, 36 Grove St., Asheville.

Oklahoma State Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Ben H. Nicholson, 301 W. 12th St., Oklahoma City.

South Carolina Pediatric Society

President: Dr. Leland B. Salters, 317 S. Warley St., Florence.
Secretary-Treasurer: Dr. D. Lesesne Smith Jr., 187 Oakland Ave., Spartanburg.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Eugene Rosamond, 1074 Madison Ave., Memphis.
Secretary: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Place: Nashville. Time: April 12-14, 1938.

TEXAS PEDIATRIC SOCIETY

President: Dr. John G. Young, 3930 McKinney Ave., Dallas.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Galveston. Time: May 10-12, 1938.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. W. Ambrose McGee, 616 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, Medical Arts Bldg., Roanoke.
Place: Danville, Va. Time: October 1938.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Claude L. Holland, 400 Locust Ave., Fairmont.
Secretary: Dr. Theresa O. Snaith, Weston.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. William M. Champion, 2323 Prospect Ave., Cleveland.
Secretary: Dr. Arthur J. Horesh, 10515 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. T. B. Verner, 170 St. George St., Toronto.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto.

BRONX PEDIATRIC SOCIETY

President: Dr. Samuel Tripler, 1555 Grand Concourse, New York.
Secretary: Dr. Harry S. Altman, 940 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Walter D. Ludlum, 1421 Cortelyou Rd., Brooklyn.
Secretary: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank Vasder Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

CHICAGO PEDIATRIC SOCIETY

President: Dr. C. A. Aldrich, 723 Elm St., Winnetka, Ill.
Secretary: Dr. George F. Munns, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave., Chicago. Time: Third Tuesday of each month, October to May, inclusive.

DALLAS PEDIATRIC SOCIETY

President: Dr. John Young, 3930 McKinney Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3622 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. W. J. Scott, 5140—2d Ave., Detroit.
Secretary: Dr. Harold E. Clark, 100 Atkinson Ave., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. T. F. Davenport, 104 Ponce de Leon Ave., Atlanta.
Secretary: Dr. James P. Hanner, 384 Peachtree St., Atlanta.
Place: Academy of Medicine, 38 Prescott St., N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Walter F. Qualtrough, 920 Westheimer Ave., Houston, Texas.
Secretary-Treasurer: Dr. Allan Penny Bloxsom, 4402 Travis St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385—24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 1020 Boston Bldg., Salt Lake City, Utah.
Place: Salt Lake City, General Hospital. Time: First Thursday of each month, 8 p. m.

Kansas City (Missouri) Pediatric Society

President: Dr. W. R. Moore, 620 Francis St., St. Joseph.
Secretary: Dr. F. S. Hogue, 1103 Grand Ave., Kansas City.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Edwin F. Patton, 3875 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Henry F. Gallagher, 1930 Wilshire Blvd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd.
Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Harry R. Litchfield, 163 Eastern Parkway, Brooklyn.
Secretary: Dr. Jacob Rosenblum, 550 Ocean Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: Third Wednesday of each month, October to May.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. W. C. A. Steffen, 42 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144—38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May

Memphis Pediatric Society

President: Dr. Clyde V. Croswell, 1052 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. David W. Goltman, 1073 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. Joseph Shimpa, 2309 N. 36th St., Milwaukee.
Secretary: Dr. Helen Jane Zillmer, 781 N. Jefferson St., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New England Pediatric Society

President: Dr. Henry E. Utter, 122 Waterman St., Providence, R. I.
Secretary-Treasurer: Dr. Henry E. Gallup, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Samuel Z. Levine, 525 E. 68th St., New York.
Secretary: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northwestern Pediatric Society

President: Dr. Roger L. J. Kennedy, Mayo Clinic, Rochester, Minn.
Secretary-Treasurer: Dr. Robert Rosenthal, 437 Lowry Medical Arts Bldg., St. Paul.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Time: Alternate months.

Philadelphia Pediatric Society

President: Dr. Emily Bacon, 2104 Spruce St., Philadelphia.
Secretary: Dr. James E. Bowman, 4091 Comly St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to June, inclusive.

Pittsburgh Pediatric Society

President: Dr. James LeRoy Foster, Highland Bldg., Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200—5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to April, inclusive.

Richmond Pediatric Society

President: Dr. A. S. Hurt, 1028 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. Louise Fry Galvin, 2416 Stuart Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: First Thursday of each month (except July, August and September).

Rochester Pediatric Society

President: Dr. J. Merrel Parker, 11 N. Goodman St., Rochester, N. Y.
Secretary: Dr. H. C. Soule, 16 N. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month.

Rocky Mountain Pediatric Society

President: Dr. James E. Russell Jr., 820 Metropolitan Bldg., Denver.
Secretary: Dr. F. Craig Johnson, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 2:30 p. m.

St. Louis Pediatric Society

President: Dr. John Zahorsky, 536 N. Taylor Ave., St. Louis.
Secretary-Treasurer: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society. Time: Third Friday of every month.

Seattle Pediatric Society

President: Dr. Frank H. Douglass, Medical Dental Bldg., Seattle.
Secretary: Dr. C. Luverne Smith, Stimson Bldg., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Louis M. Earle, 6381 Hollywood Blvd., Los Angeles.
Secretary: Dr. Philip E. Rothman, 3875 Wilshire Blvd., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Damon O. Walthall, 1103 Grand Ave., Kansas City, Mo.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. R. A. Higgons, 264 King St., Port Chester, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 131 Purchase St., Rye, N. Y.
Place: Grasslands Hospital. Time: Third Thursday in October, December, February and April.